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PROJECT STATUS REPORTS

MARCH, 1993

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PROJECT STATUS REPORTS

MARCH, 1993

CENTER FOR INDOOR AIR RESEARCH
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Modeling NO_2 Dosimetry in the Lung

PI: Satish Anjilvel, Ph.D.
Department of Medicine
Duke University Medical Center

The investigative team will develop a series of increasingly complex dosimetry models describing gas transport and uptake in lung components and blood to predict site-specific dose on a microscopic scale. The complex models which predict dose at probable sites of focal injury may allow one to deduce human risk from animal studies.

Contract No.	91-01	91-01A
Contract Execution Date	1/10/91	12/30/91
Contract End Date	1/09/92	12/29/92
No Cost Extension		3/92
Budget	$84,141	$65,873
Budget Amendment		
Five month report due	6/91	5/92
Five month report received	7/91	6/92
Site visit (anticipated)		
Site visit (conducted)	5/8/91	
Ten month report due	11/91	12/92 final
Ten month report received		3/92 draft final
Continuation approved		

STATUS: August 1991

Project is progressing on schedule in three areas. PI has developed a method for determining the effective dispersion coefficient in alveolar ducts, has developed a more accurate than proposed scheme for flows in the lung's small airways, and has obtained data on rat and human lung structure for use in the development of a one-dimensional NO_2 dosimetry model.

STATUS: January 1992

The investigators have solved the Navier-Stoles equations in two-dimensional domains that represent terminal bronchioles and alveolar ducts. For their one dimensional model, they have analytically derived

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the transport coefficients for a reactive gas in air flowing through a cylindrical tube, the result of which is a generalization of effective dispersion for an inert gas. Preliminary calculations with this model indicate that the total uptake by an individual pulmonary acinus can be modeled by treating the acinus as a single compartment and that uptake throughout the entire tracheo-bronchial tree of a lobe of the rat lung can be modeled practically.

STATUS: September 1992

Progress is satisfactory. PI is continuing development of models of dosimetry of NO_2 in the lung. A multiple path model of the entire lung is being expanded and refined to examine effects of the asymmetry of the pulmonary branching pattern, an important effect identified in recent collaborative efforts with Duke colleagues in structural effects on reactive gas uptake. PI is also developing a simpler model of reactive gas dosimetry for use by researchers in the field of respiratory toxicology, which is the next step above the commonly used symmetric models.

STATUS: March 1993

The PI has defined the effective parameters for one-dimensional diffusion of a gas of low reactivity. The effective parameters are reactivity, air velocity, and diffusivity.
The rate of diffusion through alveolar ducts is affected by the presence of alveoli. The PI has determined diffusivity using a random walk method. The results are in good agreement with an analytically determined dispersion by others.
The PI developed a model of NO_2 dosimetry for the entire lung, based on a random walk solution of the one-dimensional mass transport equation. Results of applying the model to uptake by rat and human lung are that the shape of the uptake curve for rat lung is very different from that for human lung.
The PI developed a numerical method for solving the time-dependent Navier-Stokes equations for incompressible fluid flow in alveolar ducts. Velocity profiles calculated by this method were used to compute the concentration profile and uptake of an inspired reactive gas. For NO_2, the concentration profile is nearly uniform in the radial direction. Therefore, air flow patterns are not directly responsible for focal damage observed at the first alveolar duct bifurcation. Susceptibility of these cells may be enhanced by increased particle deposition here.

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Anjilvel S

Publications, Abstracts, and Presentations supported by CIAR

1. Anjilvel S, RR Mercer and FJ Miller. 1993. Development of improved computer simulation models of fiber transport and deposition in alveolar ducts. Ann Occup Hyg. In press.

2. Anjilvel S, RR Mercer and JD Crapo. 1992. A computational model of particle deposition in alveoli and alveolar ducts. Submitted to American Lung Association Annual Meeting.

3. Anjilvel S. 1992. Chorin's projection method for the Navier-Stokes Equations in an arbitrary domain. Submitted to J. Comp. Phys.

4. Anjilvel S, RR Mercer and JD Crapo. 1992. Effective transport coefficients of gas in the lung. In prep.

5. Mercer RR, S Anjilvel, et al. 1991. Inhomogeneity of ventilatory unit volume and its effect on reactive gas uptake. J Appl Physiol 70:2193-2205.

6. Anjilvel S, RR Mercer and JD Crapo. 1991. Calculation of the effective dispersion coefficient in alveoli and alveolar ducts. Am Rev Respir Dis 143:A765 (Abstract).

7. Anjilvel S. 1993. Transport coefficients for a reactive solute flowing in a tube. Chem Engng Sci. Submitted.

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Indoor Fate and Transformations of Selected Nitrogenous Organic Compounds

PI: Janet Arey, Ph.D.
University of California, Riverside
Statewide Pollution Research Center

The researchers will study the physical chemistry of important nitrogen-containing compounds found in indoor air, including under normal indoor lighting conditions. They will begin to develop a database for indoor air constituents.

Contract No.	90-005	90-005A
Contract Execution Date	2/6/90	7/8/91
Contract End Date	2/6/91	7/7/92
No Cost Extension	6/30/91	12/31/92
Budget	$118,814	$119,940
Budget Amendment		
Five month report due	12/90	6/92
Five month report received	1/2/91	3/92 brief communication
Site visit (anticipated) Site visit (conducted)	7/12/90	1/27/92
Ten month report due	5/91	2/93 final
Ten month report received 3/93 draft final	5/7/91	
Continuation approved	7/8/91	

STATUS: August 1991

Project is on schedule with no anticipated delays. PI has worked out the kinetics and products of the photolysis and gas-phase reactions of 2-vinylpyridine with NO_2 and Oh radicals, and has established that ozone reacts with (and has identified products from) six of eleven compounds proposed for study: 2-vinylpyridine, indole, nicotine, 2-(dimethylamino)ethanol, dimethylamine, and trimethylamine. PI is proceeding to verify FT-IR identification of products with GC/MS. She will investigate the gas-phase reactions under normal indoor lighting conditions and measure the OH radical concentration in typical office environments to assess the importance of OH radical reactions.

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STATUS: January 1992

Project and report are behind schedule by a couple of months due to increased academic commitments of the PI and co-investigator.

STATUS: September 1992

A manuscript detailing work with 2-vinylpyridine which compares its gas-phase chemistry with styrene is near completion for submission to ES&T. A new 6000 L Teflon chamber was constructed and used for experiments with cool-white fluorescence lamps to investigate the indoor photolysis of pyridine, 2-vinylpyridine, quinoline, isoquinoline, 1- and 2-nitronaphthalene, indole and nicotine. Investigations of the gas-phase chemistry of indole, quinoline, and isoquinoline with hydroxyl radicals, ozone, and nitrogen dioxide under black-lamps are underway.
PI is late with formal report of these data and preliminary results.
Report should be available Oct. 3.

STATUS: March 1993

Final report approved.
No reactions of 2-vinylpyridine, indole, quinoline or isoquinoline with NO_2 were observed, nor was any reaction of O_3 with quinoline or isoquinoline observed. Rate constants for the OH radical reactions with 2-vinylpyridine, indole, quinoline, isoquinoline and nicotine, of NO_3 radicals with indole, and of O_3 with 2-vinylpyridine, indole, nicotine, methylamine, dimethylamine, trimethylamine, 2-(dimethylamino)ethanol and tetramethylhydrazine were determined at room temperature and the products of certain of these reactions studied at room temperature and one atm total pressure of air. The rate constants for the reactions studied, together with those from previous literature studies, were combined with estimated concentrations of OH radicals, NO_3 radicals, NO_2 and O_3, and indoor and outdoor light intensities and spectral distributions, to calculate the lifetimes of the nitrogen-containing organic compounds studied. For pyridine, 2-vinylpyridine, quinoline, isoquinoline and the nitronaphthalenes, the known gas-phase reactive loss processes are fairly long (several hours) and air exchange may be the most important indoor removal process for these compounds. The chemical loss processes identified and studied here all lead to fairly long lifetimes, apart from the NO_3 radical reaction with indole. NO_3 radical as well as gaseous nitric acid reactions with several of these compounds could potentially be important reactive loss processes. These could not be studied with the available experimental methods.

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ETS: Nasal Response and Aerosol Deposition Effect

PI: **Rebecca Bascom, M.D.**
University of Maryland
Department of Medicine

The researchers will use acoustic rhinometry to assess upper respiratory effects of sidestream smoke, predict alterations in deposition of secondary pollutants, and characterize the efficacy of a portable room air cleaner in ameliorating the effects of ETS.

Contract No.	90-30	90-30A	90-30B
Contract Execution Date	10/1/90	10/1/91	10/1/92
Contract End Date	10/1/91	10/1/92	10/1/93
No Cost Extension			
Budget	$160,686	$142,029	$156,168
Budget Amendment			
Five month report due	3/1/91	3/1/92	3/1/93
Five month report rec	4/1/91	2/27/92	4/8/93
Site visit (anticipated)			
Site visit (conducted)	Informal visit with Roger Jenkins 9/24/90 Formal visits - 7/15/91, 7/29/92		
Ten month report due	8/1/91	8/1/92	
Ten month report rec.	7/22/91	8/3/92	
Continuation approved			
Final report due			10/1/93
Final report rec.			

STATUS: August 1991

Methods development has proceeded on schedule and has included a revision of the exposure system, development of the acoustic rhinometry system and upgrading and streamlining of the posterior rhinomanometry system. The PI has completed the human challenge studies and has verified and entered all data on spread sheets. The current statistical analysis is focusing on

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three areas: 1) to determine the effect of STS on the upper airway; 2) to correlate results from acoustic rhinometry with symptoms and posterior rhinometry; and 3) to analyze models of upper airway physiology using these data. Statistical analysis should be completed within one month, with subsequent completion of abstracts and manuscripts.

Findings have indicated that controlled exposure to sidestream tobacco smoke causes symptoms of mucosal irritation and nasal conjestion. Nasal resistance increases, and is associated with a reduction of nasal volume throughout the nasal cavity including the narrowest anterior segment. These findings are apparent with exposure to STS at 15 ppm CO for one hour. Further statistical analysis will allow interpretation of results at lower concentrations of STS, but the average response to STS at 1ppm and 5ppm CO is much smaller than the response at 15 ppm CO and there does not appear to be a dose-response relationship at the lower doses. A range of symptomatic and physiologic responses was observed between subjects. Responses appear similar between groups of subjects with and without history of ETS-sensitivity, although the greatest individual changes were observed in historically sensitive individuals. Project is on schedule.

JANUARY, 1992

The papers based on the studies in year one are in preparation and will utilize the new graphics capabilities developed by the investigator. Completion of the figures are expected soon. The major data analysis has been completed, but additional analyses are being requested from the statistician. The final focus of his analysis, nearing completion, is to describe the validity of the acoustic rhinometry system.

The acoustic rhinometry experiments are proceeding smoothly. The smoke generation system at Johns Hopkins is now functional and is being plumbed to the exposure chamber. The Hopkins nasal resistance system is being tested by the biomedical engineer from U of M. Human challenges are expected to begin at Hopkins in March. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Response to Environmental Tobacco: Dose-Response Studies and the Effect on Acoustic Rhinometry," R. Bascom, T.K. Fitzgerald, T. Permutt, L. Sauder, J. Nadarajah, and D.L. Swift, abstract submitted to the American Thoracic Society / American Lung Association Annual Meeting, May 17-20, 1992, Miami Beach, Florida.

2. "Acoustic Rhinometry as a Tool for Human Inhalation Toxicology Studies," D.L. Swift, J. Nadarajah, T.K. Fitzgerald, T. Permutt, and R. Bascom, abstract submitted to the American Industrial Hygiene Conference Exposition, May 30-June 5, 1992, Boston, Massachusetts.

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Acoustic rhinometry (AR) has been used to determine the anatomic changes responsible for the physiologic response to STS in the upper respiratory tract. While nasal congestion was demonstrated by posterior rhinomanometry (NAR) only at the highest concentration of STS (15 ppm CO), acoustic rhinometry showed significant changes in mid-nasal volume at 1 and 5 ppm CO. The measured minimum nasal airway cross-sectional area by AR showed changes at all levels of cigarette smoke in a dose dependent fashion. The measured replicate values of area-distance obtained by AR were reproducible enough to yield statistically significant changes when the mean value decrements were as little as 10%. These data suggest that acoustic rhinometry is a sensitive indicator of the nasal congestive response to STS.

With regard to determining the effects of ETS exposure on the distribution and fate of secondary particulate pollutants in the respiratory tract, all experimental methods have been developed, subject recruitment has been completed, and challenges have taken place. Nasal aerosol deposition studies are performed using a polydispersed aerosol of diethylhexylsebacate. The particles are directed through the nose at a fixed flow rate while subjects hold their breath for twenty seconds. Air enters the nose, passes through the nasopharynx, and exists the mouth. Baseline particles are enumerated for the size range 0.5-7 microns, and the number and size of particles is again enumerated after exiting through the mouth. The fractional removal at each size range is calculated. Nasal particle clearance studies utilize the radioactive aerosol colloidal Tc^{99m}-sulfur in normal saline solution, which is sprayed onto the nasal mucosa just posterior to the nasal valve. Following this, the subject places his or her face against a scintillation detector for serial counts measurements. The analysis of the study results is being completed.

Work in underway to begin assessing the efficacy of commercially available room air cleaners in reducing the response to ETS in sensitive subjects. Project is on schedule.

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The PI completed a series of exposure experiments in twelve adult human subjects, six sensitive and six non-sensitive, in which a one hour exposure to smoke associated with 15 ppm CO was followed by measurement of nasal mucociliary clearance for a period of 60 minutes after placement of a radio-labelled liquid bolus at the anterior nasal turbinate zone.

Comparison of nasal clearance rates with control values in the non-sensitive individuals showed a marked increase in mucociliary clearance rate which was particularly evident in the first 15 minutes. Three sensitive individuals showed similar increases in clearance rate, while three showed decreased clearance rate. Measurements of the particle deposition efficiency of the nasal passage made similarly before and after the ETS exposure showed no effect despite dimensional changes at the level of the nasal valve. The PI concludes that this level of ETS can produce changes in mucociliary clearance rate in non-smoking individuals which can markedly alter the uptake and fate of inhaled particle and vapors by changing the residue time of such substances in the nasal airways.

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With regard to Aim 3, characterizing the efficacy of a portable room air cleaner, the PI has been advertising for, screening, and performing qualifying STS challenges to identify appropriate subjects. She has performed preliminary interviews on 45 subjects, extended qualifying interviews on 12 subjects, and smoke challenges on 4 subjects, with an additional 4 subjects scheduled for mid-April. Project is somewhat behind schedule.

Associated Manuscripts and Abstracts/Presentations

1. "The Effect of Environmental Tobacco Smoke on Nasal Clearance in Sensitive and Non-Sensitive Human Subjects," D.L. Swift, S. Nadarajah, K.H. Cheng, M.A. Bickert, R. Bascom. T.K. Fitzgerald, and T. Permutt, abstract submitted to the American Industrial Hygiene Conference & Exposition, May 15-21, 1993, New Orleans, Louisiana.

2. "Sidestream Tobacco Smoke (STS) Alters Regional Nasal Mucociliary Clearance: Comparison of Sensitive and Nonsensitive Subjects," J. Nadarajah, R. Bascom. T.K. Fitzgerald, M. Bickert, K. Cheng, T. Permutt and D. Swift, abstract submitted to the 1993 American Lung Association / American Thoracic Society International Conference, May 16-19, 1993, San Francisco, California.

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Adhesion of Dust Mite Allergen to Carpeted Surfaces

PI: Patrick N. Breysse, Ph.D.
Johns Hopkins University School of Public Health

The investigators will evaluate factors which affect the adhesion of dust mite allergens to different types of carpet commonly found in homes and offices, to test the hypothesis that the amount of allergen-containing dust recovered from carpets is correlated to the carpet's adhesive characteristics. Results of the work will lend information on how adhesion of allergen to fabric surfaces may affect resuspension and ultimately human exposure.

Contract No.	93-05	
Contract Execution Date	1/1/93	
Contract End Date	12/31/93	
No Cost Extension		
Budget	$87,918	$39,085
Budget Amendment		
Five month report due	5/93	
Five month report received		
Site visit (anticipated)		
Site visit (conducted)		
Ten month report due	10/93	
Ten month report received		
Continuation approved		

STATUS: March 1993

Contract fully executed 2/19/93.

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Filter Cassette Sampling for Biological Aerosols
PI: Harriet A. Burge, Ph.D.
University of Michigan

The investigators will explore the potential of filter cassette sampling for viable and particulate bioaerosols in laboratory chamber and pilot field studies. Methodologies include particle enumeration, germination tests, and culture. The researchers also will explore the feasibility of cassette-based immunoassays for mycotoxins, and develop useful protocols for research involving bioaerosol sampling.

Contract No.	91-06	91-06A	
Contract Execution Date	1/24/91	1/30/92	2/1/93
Contract End Date	1/23/92	1/31/93	1/31/94
No Cost Extension			
Budget	$144,098	$136,433	$150,000
Budget Amendment			
Five month report due	7/91	6/92	7/93
Five month report received	7/15/91		
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	12/91	11/92	final 2/94
Ten month report received		11/92	
Continuation approved	1/28/92	12/92	

STATUS: August 1991

Project is progressing successfully on schedule. PI is calculating a mycotoxin risk analysis for aflatoxin and satratoxin exposure based on spore toxin content to be compared to epidemiological literature. Its publication is anticipated within six months. PI has performed cultural analysis of 51 filter cassette samples to determine requirements for accurate assessments of colony counts. PI is engaged in microscopic evaluation of filter cassette samples to evaluate fluorescence for bacteria and fungus spores counting and to evaluate inter-counter error. Mite antigen assays have been reinstituted for field sample testing in the near future.

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STATUS: January 1992

Preliminary counting efforts of spores on closed-faced filters demonstrate that spores are concentrated in the center of closed-faced collectors, and more evenly distributed in open-faced devices.
Experiments to test the feasibility of using acridine orange for evaluating fungus spore levels have borne out that fungus material containing melanin does not fluoresce with acridine orange, and that fungal spore shape and wall characteristics often are not apparent with this stain.
PI was unable to detect mite antigen on filter air samples collected during vacuuming with their mite ELISA (DL=0.5 ng/mL). PI is investigating if assay is sufficiently sensitive to detect mite antigen at levels at which the antigen induces symptoms or sensitization.

STATUS: September 1992

PI is late with report. Report is expected Oct. 1. An update on data or results of this project will be available after this date.

STATUS: March 1993

Preliminary results of viability experiments with Penicillium chrysogenum show that filter cassettes are useful for sampling some viable fungus spore aerosols.
Results from experiments comparing cultural and acridine orange bacterial counting show that the two counting methods are correlated but acridine orange counts are consistently higher by an order of magnitude.
Results of experiments comparing bacterial counts and endotoxin show a weak correlation and that bacterial counts alone do not accurately represent endotoxin levels.
Field studies using the filter cassette system in indoor environments are underway.

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Burge HA

Publications, Abstracts, and Presentations Supported by CIAR

1. Burge HA. 1992. Some comments on biological aerosols in the occupational environment. Presented at and published in proceedings of the International Occupational Health Society meeting, Brussels, Belgium.

2. Su HJ, JD Spengler and HA Burge. 1993. A study of possible interactions between airborne fungi, suspended particulates (SFP), and nitrogen dioxide (NO_2) and their role in childhood respiratory symptoms. Accepted for presentation and publication in proceedings of Indoor Air '93, Helsinki, Finland, July 4-8.

3. Burge HA, M Muilenberg and T Sweet. 1993. Hypersensitivity pneumonitis associated with exposure to acid-fast bacilli in machining fluid aerosols. Submitted to Indoor Air '93, Helsinki, Finland, July 4-8.

4. Muilenberg ML, TM Sweet and HA Burge. 1993. A comparison of methods for estimating bacterial levels in machining oil mists. Submitted to the American Academy of Allergy for the 1993 annual meeting.

5. Pan PM, HA Burge and ML Muilenberg. 1993. Bacterial content of machining fluids and associated aerosols. Submitted to the American Academy of Allergy for the 1993 annual meeting.

6. Burge HA, W Burge and M Muilenberg. 1993. Distribution of culturable fungi in carpet dust samples across the USA. Submitted to the American Academy of Allergy for the 1993 annual meeting.

7. Su JH, ML Muilenberg and HA Burge. 1993. Problems associated with the establishment of fungal exposure guidelines. Submitted to the American Academy of Allergy for the 1993 annual meeting.

8. Muilenberg ML, RA Aqwwr, PM Pan and HA Burge. 1992. Filter cassette sampling for fungus aerosols. Presented at an international conference on the establishment of guidelines for fungus aerosol exposure in Baarn.

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Respiratory Toxicology of Kerosene Space Heater Emissions

PI: Lung Chi Chen, Ph.D.
Department of Environmental Medicine
New York University Medical Center

The researchers will investigate the effects of particulate and vapor emissions from kerosene space heaters on pulmonary function and alveolar macrophages in guinea pigs. Effects of exposure to kerosene heater emissions will be compared to those of exposure to a model acidic aerosol atmosphere. The effects of animal age on any observed respiratory effects from kerosene space heaters will be studied.

Contract No.	92-04	92-04A	
Contract Execution Date	1/13/92	1/1/93	
Contract End Date	1/12/93	12/31/93	
No Cost Extension			
Budget	$163,910	$149,987	$159,884
Amendment		Budget	
Progress report due	6/92	5/93	
Progress report received	6/92		
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	11/92	10/93	
Ten month report received	10/92		
Continuation approved			

STATUS: January 1992

Contract executed.

STATUS: September 1992

Emissions from the kerosene space heater were characterized according to particle number concentration, total sulfate and nitrate, and NO_x concentration in the exposure chamber as a function of wick height. Work is progressing on characterizing the emissions to measure nitric acid, pH, and hygroscopicity of the aerosol.

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STATUS: March 1993

There were no significant changes in any of the biochemical parameters tested in the lavage fluid except for protein concentration after 4-wk exposure. Alveolar macrophage function alterations were observed. Intracellular pH of lavaged cells was depressed by 0.06 pH units after 4-day exposure. In vitro phagocytic function of alveolar macrophages was enhanced by 51%. After 4-wk exposure, Ca^{2+} concentration was elevated by 85% above the control level. Short term exposures to kerosene space heater emissions at concentrations normally encountered in home use can produce alterations in guinea pig alveolar macrophages, most likely due to the ultrafine sulfuric acid particle component of the emissions.

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Chen LC

Publications, Abstracts, and Presentations Supported by CIAR

1. Chen LC, T Gordon, M Ryan and Q Qu. 1993. Respiratory effect of kerosene space heater emissions. Abstract presented at the annual meeting of the Society of Toxicology, New Orleans, LA, March.

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Air and Contaminant Flow Study for Improving Ventilation Design of Partitioned Office Rooms

PI: **Leslie L. Christianson, Ph.D., P.E.**
University of Illinois at Urbana-Champaign
Department of Agricultural Engineering

In the proposed project, 11 standard test conditions (2 room configurations, 3 air diffusers, 2 air flows) which represent typical commercial rooms with privacy screens, furniture and thermal and contaminant sources under realistic ventilation conditions, will be defined. Air velocity, temperature and turbulent characteristics will be measured at the boundaries as well as within the room under precisely controlled conditions and compared with ones for the rooms without obstructions. These detailed measurements in the Room Ventilation Simulator at the University of Illinois will provide information on the influence of obstructions in the rooms of commercial buildings and provide a data base for developing a numerical simulation model.

Contract No.	93-06	
Contract Exec Date	3/12/93	
Contract End Date	3/12/94	
No Cost Extension		
Budget	$64,869	$47,369
Budget Amendment		
Five month report due	8/12/93	
Five month report rec		
Site visit (anticipated)		
Site visit (conducted)		
Ten month report due	1/12/94	
Ten month report rec		
Continuation approved		

STATUS: MARCH, 1993

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Predicting Inspiration Efficiency of Blunt Body Samplers in Aerosol Polluted Indoor Air

Postdoctoral Fellow: I-Ping Chung, PH.D.
Dept. of Mechanical & Aerospace Engineering
University of California, Irvine

The objective of this work is to theoretically investigate the sampling efficiencies of a blunt body sampler (similar to the shape of a human head) in calm air by numerical calculation. The results will include the investigation of affecting parameters, such as orientation, suction velocities, opening sizes, particle sizes, etc., and the comparison of the previous experimental data and the ACGIH curve with the numerical results. Subsequently, the postdoc will design and construct the experimental apparatus. The experimental results will be used to verify the validity of her theoretical calculations.

Fellowship Year	'92-'93
Start Date	4/1/92
End Date	3/31/93
Budget	$30,000
Reports received	2/22/93

STATUS: MARCH, 1993

Numerical calcualtions have nearly been completed after first modifying the numerical code to solve the velocity field in indoor air conditions. The gravity force has also been included in the numerical code for solving particle trajectories at different orientations.

Results on the study of a cylindrical sampler show that the sampler bluntness and orientation have important effects on aspiration efficiency. In particular, a blunt sampler usually has higher aspiration efficiency than does a sharp-edged sampler. This result suggests that one needs to be careful interpreting the indoor environmental aerosol concentration measurements carried out by a thin-walled tube sampler. A human head, which is more similar to a blunt sampler than to a thin-walled tube, may inhale more particles than indicated by environmental aerosol measurements. The results of the cylindrical sampler calculation indicate the importance of comparing the aspiration efficiency between a tube sampler and a spherical blunt sampler in calm air. So far, the velocity field for the spherical sampler with a circular opening has been successfully calculated and the particle trajectories are being computed. The study of the spherical sampler will provide more geometrically reasonable information about human inhalability in aerosol polluted indoor air, however, preliminary results indicate that the cylindrical sampler gives the same trends and general conclusions.

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Associated Manuscripts and Abstracts/Presentations

1. Chung, I. and Dunn-Rankin, D. "The Effects of Bluntness and Orientation on Two-Dimensional Samplers in Calm Air," submitted to Aerosol Science and Technology.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Charcoal smoke and Risk of Respiratory Infections
PI: Adolfo Correa-Villasenor, M.D., Ph.D.
Johns Hopkins School of Hygiene and Public Health

The investigators will assess the effect of indoor charcoal smoke pollution on acute respiratory infections (ARI) in children. In a concurrent prospective study among Santo Domingo's children population, exposure and ARI data will be gathered by parent interview, environmental measurements, and child examination. The information on the impact of indoor charcoal smoke in lower and upper respiratory infections in children may be useful in selecting preventive strategies for ARI.

Contract No.	91-04	91-04A
Contract Execution Date	5/17/91	6/1/92
Contract End Date	5/16/92	5/31/93
No Cost Extension		
Budget	$213,815	$219,466
Budget Amendment		
Five month report due	10/91	10/92
Five month report received	12/91	12/92
Site visit (anticipated)		
Site visit (conducted)	2/26/92	
Ten month report due	3/92	Final 5/93
Ten month report received	4/92	
Continuation approved	5/92	

STATUS: August 1991

PI has developed questionnaire, is training interviewers, and has begun constructing the sample frame and selecting samples. PI is currently developing a data management system that readily allows for communication between the US and Santo Domingo.

STATUS: January 1992

Three field surveys have been conducted to identify neighborhoods where cooking with charcoal was common, eligible households within these

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neighborhoods, and defining the sampling frame for selection of study subjects. The study population has been identified and subject recruitment is nearly complete.

STATUS: September 1992

Forty additional children of comparable exposure and age to those lost to follow-up since last status were enrolled.
Preliminary results on environmental measurements - NO_2 levels are very low. Wood charcoal homes have slightly higher airborne respirable dust concentrations.
Preliminary results on occurrence of ARI - After 10 weeks of follow-up, the unadjusted cumulative frequency of ARI was 7.7% (4.4% URI and 3.3% LRI). The unadjusted cumulative frequency of ARI among children living in charcoal-using households was 7.3% while that among children living in propane gas-using households was 8.1%. The ratio of cumulative frequencies was 0.9. Additional follow-up, inclusion of reported ARI episodes, adjustment for confounders and use of quantitative exposure indices based on environmental measurements are underway and will provide for assessment of the association between ARI and charcoal smoke exposure.

STATUS: March 1993

The field work including questionnaire data entry was completed in December 1992. All environmental samples collected during the last months of the field work were analyzed at JHU and the results entered into a computer file. PI has been editing both epidemiologic and environmental data files and updating epi data files as needed. Presently, PI is conducting exploratory data analysis and starting to work on final report.

250400653274

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Effect of ETS and NO2 on Respiratory Infection: Murine Model Development

PI: Jerry K. Davis, Ph.D.
University of Alabama, Birmingham
Department of Comparative Medicine

This work will explore how the potential effects of ETS and/or NO2 alter susceptibility to bacterial and viral infections. This study will determine the effects of these indoor air constituents on the severity rather than on the incidence of infection.

Contract No.	90-004		90-004A	90-004B
Contract Execution Date	2/2/90		3/8/91	3/8/92
Contract End Date	2/2/91		3/8/92	3/8/93
No Cost Extension				7/1/93
Budget	$158,383	$152,383	$166,752	
Budget Amendment				
Five month report due		NA	8/8/91	8/8/92
Five month report received		NA	8/8/91	9/21/92
Site visit (anticipated)				
Site visit (conducted)		12/18/90		
Ten month report due		12/2/90	1/8/92	
Ten month report received		2/4/91	1/21/92	
Continuation approved		end of January		
Final report due				7/1/93
Final report rec.				

STATUS: August 1991

The Kentucky smoking machine works well and all the modifications necessary for characterization of the smoke are completed. The PI has established the necessary dilutions of smoke needed to achieve a 10%, 5% and 1% COHb concentration in mice. The exposure and experimental protocols for the first experiment, which will be a 2 month exposure to ETS to give a 10% COHb concentration in vivo, followed by a 2 ppm NO_2, and infection with M. pulmonis, have been developed.

2504065375

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

A large volume of the Sendai virus stock culture was grown and the intranasal (IN) vs aerosol experiments have been completed. The experiments for determining the initial sites of replication in both IN and aerosol infection have been done and the tissues collected for both virus titers and tissue localization of virus. The PI has established an immuno-enzyme procedure for staining cell cultures (for virus titers) and tissues for virus. Also, the morphometric methods for evaluation of Sendai lesions have been completed.

There has been a delay in beginning the actual animal exposures because of an insufficient number of age matched mice. In March, all of the breeding animals had to be replaced, so the PI did not have enough mice of the correct age until the June litters were born. Since the mice must be at least 8 weeks old (young adults) for the experiments, additional time had to elapse before the start of the exposures. The breeding colony has now been expanded and the breeder retirement schedule will be adjusted to ensure the availability of sufficient numbers of mice for the remainder of the experiments.

JANUARY, 1992

1. Effects on Murine Respiratory Mycoplasmosis (MRM). Ninety-six pathogen-free, 8-10 week old, C57BL/6N mice of both sexes were divided into a control group (48 mice) and an ETS exposed group (48 mice). All mice in the exposed group were exposed for 3 hrs per day for 5 days/week for 8 weeks to sufficient ETS to induce 10% COHb in the mice. Control mice were sham exposed to ETS. After 8 weeks of ETS exposure, 24 mice from each group were exposed to 2 ppm NO_2 for 4 hours; the remaining mice in each group were sham exposed. Twelve mice of each group were exposed to aerosols of M. pulmonis generated from 5 x 10^3 CFU of viable organisms in the nebulizer; the remianing 12 were exposed to aerosols generated from 5 x 10^4 CFU.

The mice were killed 7 days PI. Serum was taken for virus and mycoplasma serologies, and respiratory tract tissues were taken for histology and mycoplasma enumeration. Individual lung lobes, tracheas, and nasal passages were scored subjectively for epithelial lesions, exudation in airways, and lymphoid infiltration. Lung lobes were also scored for alveolitis. Mild lesions typical of MRM in C57BL/6N mice were present in both the upper and lower respiratory tract of all animals, but neither exposure to simulated ETS, nor exposure to simulated ETS plus 2 ppm NO_2, increased lesion severity. Results for pneumonitis, epithelial lesions, exudation, and lymphoid infiltration are similar in that there are no significant differences between any groups.

2. Effects on Sendai virus. The protocol followed was the same as that for MRM with the difference being that disease exposed mice were exposed to aerosols of Sendai virus generated from undiluted UAB Sendai X1351 stock (Hemadsorption $TCID_{50}$ -10^4/ml). Twelve mice from each group were killed at 3 days PI and the remiander were killed at 5 days PI. On each day, 6 mice were processed for virus titers in the upper and lower respiratory tract. Tissues were taken from the remaining 6 mice for histology. Serum was taken from all mice for virus and mycoplasma

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

serology. Samples from this experiment are still being processed, and the data are not yet available. Project essentially is on schedule.

SEPTEMBER, 1992

During the last eight months, the PIs have performed the experiments necessary to determine the deposition of simulated ETS particles within the respiratory tract, determined the effect of ETS on virus numbers within the respiratory tract, and examined the effect of ETS on mycoplasma numbers in acute infection and on MRM in chronic disease.

Deposition of ETS was determined by measuring the concentration of cadmium in the nasal passages, lungs, and stomach. Mice were exposed for three hours to ETS generated from cigarettes made from tobacco that had been soaked in 50mM $CdSO_4$, and then dried at room temperature. Samples from mice were pooled to produce sufficient amounts of tissue for analyses, and cadmium concentrations were determined by atomic absorption spectrometry by SmithKline Beecham Clinical Reference Laboratories, Nashville, TN. Results show that greater than 90% of retained ETS particles were deposited in the lungs.

The PIs have completed the virus titrations from the acute Sendai experiment described previously. There was no difference in titers between animals exposed to sufficient ETS to induce 10% COHb and control animals.

In experiments involving mycoplasma numbers in acute infection (ETS to induce 10% COHb, 2ppm NO_2, and 14 day gross pneumonia doses (PD_{50} and 0.1 PD_{50} or 10^{10} CFU/ml and 10^9 CFU/ml in the nebulizer)), there were no differences in lesions or numbers of M. pulmonis in the tissues among groups infected with the higher dose. However, both ETS and NO_2 affected the distribution of organisms in mice infected with aerosols generated from 10^9 organisms in the nebulizer. At this dose, M. pulmonis was only found in the lungs of mice that had been exposed to ETS, and mice exposed to 2 ppm NO_2 had fewer M. pulmonis in the nasal passages. This reult may be due to the effects of simulated ETS on cilia motility. Currently, studies are underway to determine if the concentration of simulated ETS required to induce 5% COHb along with 10^9 CFU/ml in the nebulizer gives similar results.

In the chronic MRM studies, mice in the ETS exposed groups developed severe clinical illness within 2 weeks of initiation of ETS exposure, and 4 mice in these groups died from MRM. The experiment was terminated, and the mice sacrificed for humane reasons. At the time of sacrifice, there was no statistical difference in the incidence of gross lung lesions or in the numbers or organisms recovered from either the nasal passages or lungs between the ETS exposed and control mice, although there were more mice with gross lesions in the ETS exposed groups. Histology sections are being processed, but are not yet available. However, lung lesions appeared to be more extensive in the ETS exposed mice. This experiment is presently being repeated. Project essentially is on schedule.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

MARCH, 1993

The PI has accepted a position as the Director of the Division of Comparative Medicine and Animal Resources at the University of Florida. He has requested a six month (till July 1, 1993) extension of this project, at no cost to CIAR, to complete the data analysis and completion of the final report of this project.

2504065378

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Efficacy of copper and silver ion in disinfection for humidifiers
PI: Timothy Ford
Harvard School of Public Health

The investigators will critically evaluate the efficacy of copper/silver generation in disinfection of humidifier water. They will study disinfection in both portable ultrasonic humidifiers and in-line residential humidifiers. The research will include an evaluation of the emission of the metal ions in the water vapor/humidified air.

Contract No.	91-07	91-07A
Contract Execution Date	7/29/91	2/1/93
Contract End Date	7/28/92	1/31/94
No Cost Extension	until 1/31/93	
Budget	$70,013	$57,066
Budget Amendment		
Five month report due	1/92	6/93
Five month report received	1/92	
Site visit (anticipated)		
Site visit (conducted)	7/9/92	
Ten month report due	final 10/92	final 1/94
Ten month report received	final 11/92	
Continuation approved	12/93	

STATUS: August 1991

Contract fully executed.

STATUS: January 1992

Results to date show no evidence of a decrease in bacterial viability or numbers as a result of aerosolization. It is clear that copper and silver ion disinfection is efficient in the short term. Some of the naturally occurring bacteria, especially P. paucimobilis, are more resistant to metal toxicity than the experimental P. aeruginosa culture.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Ion concentrations need to be maintained at optimal levels and may need to be pulsed to reduce development of resistant populations. Concentrations as low as 200 ppb Cu^{++}/20 ppb Ag^{+} may provide effective disinfection against opportunistic pathogens if maintained.

STATUS: September 1992

Portable humidifiers - Metal concentrations are reduced in the humidity condensate, but by no more than a factor of two and less at the higher concentrations. Accumulation of aerosolized metals is therefore of concern.
In order to use copper and silver as an effective disinfectant for domestic humidifiers free ions must be continually produced, humidifier water frequently changed and reservoir frequently cleaned. Since the conductivity of household water is insufficient for small scale generation of biocidal concentrations of ions, or the householder's treatment of the humidifier negates the need for a biocide, the use of copper and silver does not appear to be a viable approach for disinfection in this type of humidifier.
Residential in-line humidifiers - PI has completed the development of an experimental test rig, supplying four identical residential humidifiers with flow-regulated hepa-filtered air, and containing the copper and silver flow through ion-generating unit. PI is testing the efficacy of copper and silver ion generation in disinfection of Boston tap water and against challenge organisms.

STATUS: March 1993

Residential humidifier experiments:
Rotating drum, on-line residential humidifiers will aerosolize bacteria and fungi to the air stream. There is a reduction in total numbers by 1-1.5 orders of magnitude but no apparent reduction in viable numbers, suggesting that viability increases the likelihood of aerosolization. Copper and silver ion disinfection appears to cause only a minimal decrease in total numbers of naturally occurring bacteria (<1 order of magnitude), but over time can reduce viability by several orders. Preliminary speciation analysis suggests that copper may be rapidly complexed by organic material. Minimal aerosolization of metals is apparent.

2504065380

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Ford T

Publications, Abstracts, and Presentations Supported by CIAR

1. Kay E and T Ford. 1993. Resistance of bacteria and fungi to copper and silver ions used in disinfection of ultrasonic and residential humidifiers. Abstract. To be presented at the 93rd General Meeting of the American Society for Microbiology, Atlanta, GA, May.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Chemical Markers for Bacterial Components in Indoor Air

PI: Alvin Fox, Ph.D.
University of South Carolina

Lennart Larsson, Ph.D.
University of Lund, Sweden

This study will attempt to correlate the amounts of Gram negative bacterial endotoxins (as measured by gas chromatography-mass spectrometry of the chemical markers 3-hydroxy fatty acids of the 10-20 carbon atoms and heptoses) with respiratory symptoms related to contaminated indoor air environments at worksites, schools and office buildings. In addition, the investigators plan to study the relationship between symptoms and levels of airborne cell wall peptidoglycan.

Contract No.		92-03	92-03A
Contract Execution Date		12/19/91	12/19/92
Contract End Date		12/19/92	12/19/93
No Cost Extension			
Budget	$146,802	$154,143	$161,848
Budget Amendment			
Five month report due		5/19/92	5/19/93
Five month report received		5/14/92	
Site visit (anticipated)			
Site visit (conducted)		7/15/92 (ME to Lund, Sweden)	
Ten month report due		10/19/92	10/19/93
Ten month report received		11/2/92	
Continuation approved			

STATUS: JANUARY, 1992

SEPTEMBER, 1992

Two independent procedures for GC-MS analysis of muramic acid are in place; a semi-automated alditol acetate method in Columbia and a new

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

methyl trifluoracetate method in Lund. Large amounts of organic dust have been collected from air conditioning systems in Columbia. These samples will be analyzed in both Columbia and Lund thru '92. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

Elmroth, I., Fox, A., and Larsson, L. Sensitive muramic acid analysis using gas chromatography-mass spectrometry with negative ion detection. J. Chromatogr. (submitted 1992).

MARCH, 1993

Beta hydroxy myristic acid (a chemical marker for lipopolysaccharide) has been demonstrated to be readily measurable in ug amounts of dust collected directly from indoor air with great sensitivity. Muramic acid (a chemical marker for peptidoglycan) has been successfully measured in organic dust collected from air conditioning filters. Further improvements in sensitivity of analyses will also allow measurement of muramic acid to be employed in environmental monitoring of the bacterial content of airborne dust. This represents the major goal over the next year. The PI is also determining the respective levels of Gram positive and Gram negative bacteria by correlating the levels of the chemical markers for these two groups of organisms. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Mielniczuk, Z., Mieniczuk, E., and Larsson, L. Gas chromatography-mass spectrometry methods for analysis of 2- and 3- hydroxylated fatty acids: application for endotoxin measurement (in press).

2. Fox, A. and Black, G. Identification and detection of bacteria after derivatization after gas chromatography-mass spectrometry. In: Identification of microorganisms by mass spectrometry. (Fenselau, C., Ed.). American Chemical Society (in press).

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Exposure to Nitrogen Dioxide: Effects on Human Defenses Against Respiratory Viruses

PI: **Mark W. Frampton, M.D.**
University of Rochester Medical Center
Department of Medicine

The study will examine the effects of in vivo nitrogen dioxide exposure on infectivity of lung cells using two common respiratory viruses. The emphasis will be on detecting changes in the susceptibility of bronchial epithelial cells and alveolar macrophages to infection with respiratory viruses following in vivo exposure to NO_2. Data obtained from these studies will have relevance to the effects of NO_2 exposure on human host defense, despite the uncertainties about the role of alveolar macrophages in antigen presentation.

Contract No.	93-07	(Addnl. contracts contingent upon positive human results.)
Contract Execution Date	7/1/93	
Contract End Date	7/1/94	
No Cost Extension		

Budget	$190,025	$223,363	$239,131
Budget Amendment			

Five month report due	12/1/93
Five month report rec	

Site visit (anticipated)	
Site visit (conducted)	

Ten month report due	5/1/94
Ten month report rec	
Continuation approved	

STATUS: MARCH, 1993

2504065384

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Feasibility of a Laboratory Model of Sick Building Syndrome

PI: Robert Frank, M.D.
Division of Environmental Health Engineering
Johns Hopkins University School of Hygiene and Public Health

The investigative team will perform a pilot study in which they will test the feasibility of measuring changes in physiological, biochemical, and cytological parameters that might underlie SBS and neurobehavioral performance symptoms. The pilot study involves the controlled exposure of human volunteers to volatile organic compounds. The feasibility study might lead to an investigation of the role of olfaction and other sensory cues in driving SBS to test the hypothesis that the autonomic nervous system plays a major role in modulating SBS symptoms.

Contract No.	90-32	
Contract Execution Date	12/06/90	Start date 2/06/91
Contract End Date	2/05/91	11/30/92
No Cost Extension	3 months	10 months

Budget	$16,925
Budget Amendment	

Five month report due	7/91
Five month report received	7/91

Site visit (anticipated)	
Site visit (conducted)	

Ten month report due	Final 9/92	Received 12/18/92
Ten month report received	interim progress report received 5/92.	

STATUS: August 1991

Due to a number of approved personnel changes on this project, PI is currently reconstituting environmental engineering skills and establishing collaborative links with scientists possessing necessary skills for carrying out the work. PI has modified originally proposed experimental model of SBS to include measurement of fractional retention of VOCs by the respiratory system, testing whether sighing rate can be used to assess difficult breathing symptoms, testing the role of olfaction in modulating SBS, and exploring the addition of brain glucose metabolism to the model.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

To monitor VOC exposure, PI successfully modified some on-site equipment and facilities.

STATUS: January 1992

PI obtained joint (matching) funds for this project from NIOSH, effective 6/1/91. Project will be completed and final report to CIAR will be submitted in 9/92. Investigators have completed developing the methodology to study fractional uptake of mixed VOC, body burden, and excretion over time. They currently are developing a model to expose eyes only to an irritant VOC so as to correlate the development of subjective complaints with the content of tear fluid. They are planning studies of the learning curve on three neurobehavioral tasks that will be implemented in later phases of the research prior to beginning the whole body chamber studies.

STATUS: Septmember 1992

Progress is good. Feasibility study is on schedule.
Fractional uptake - From a small number of inhalation exposures to toluene and n-hexane, there was no consistent association between the size of the alveolar component in expired gas and the fractional uptake (or conversely, expired gas VOC concentration).
Post exposure respiratory excretion of toluene was biphasic in character. There was an initial brief phase of rapidly declining excretion lasting minutes, followed by a more prolonged phase of excretion at a low rate. For n-hexane, a rapid short-lived excretory phase was observed, but not a slow phase, perhaps reflecting limited analytical sensitivity. These findings suggest that expired gas samples may not provide reliable quantitative information on VOC exposure.
Eye irritation exposure - PI is developing a simple, semi-quantitative method for tear collection for use in testing the association between eye irritation symptoms and changes in tear fluid composition.
Effects of learning on neurobehavioral task performance - Six of eight recruited subjects have completed trials on performing three neurobehavioral tasks. Data from the completed study will indicate the number of practice trials needed to minimize the effects of learning on performance during chamber studies.

STATUS: March 1993

Final report approved 1/93.
Results summary:
Eye irritation exposure: The most intense symptom reports were associated with apparent increases in both total proteins and LDH; however, symptoms were not significant predictors of changes of these. Total proteins may be a more sensitive index of eye irritation than LDH.
Effects of VOC on neurobehavioral performance and subjective complaints: Results with both neurobehavioral tasks in conjunction with the predominance of symptoms referable to the nervous system appear to implicate the nervous system, particularly the brain, as a target site for VOC in realistic concentrations. Gradual development of symptoms in number and intensity in MCS subjects following VOC exposure, peaking at a time when odor intensity was likely to be reduced, occured. This result

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

does not support the sensory hypothesis that symptom number and intensity is a simple function of odor perception.

Reproducibilities of a Dual-Detector Probe System for Monitoring Metabolism in the CNS: The procedure was found to be excessively confining and uncomfortable as the subject is immobilized for 100 min. However, the procedure could be shortened and reproducibility improved by following an initial bolus injection with a continuous infusion of radiotracer.

2504065387

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Effects of O_3, NO_2 on Pulmonary Function & Eicosanoid Metabolism

PI: Albert Gunnison, Ph.D.
NYU Medical Center
Department of Environmental Medicine

The researchers will characterize the effects of ozone and other indoor air pollutants on pulmonary function and lung eicosanoid metabolism. Their new approach may help identify sensitive populations of individuals who are susceptible to low levels of ozone in indoor air environments.

Contract No.	90-007	90-007A	90-007B
Contract Execution Date	2/26/90	1/1/91	1/1/92
Contract End Date	2/26/91	12/31/91	12/31/92
No Cost Extension			4/30/93
Budget	$174,470	$162,306	$181,407
Budget Amendment			
Five month report due	9/90	5/91	5/92
Five month report received	10/02/90	8/91	6/92
Site visit (anticipated)			
Site visit (conducted)	6/26/90		
Ten month report due	3/91	10/91	FINAL 5/93
Ten month report received	2/18/91	1/92	
Continuation approved	3/18/91	1/28/92	

STATUS: August 1991

Project is progressing on schedule. Using a rat model, PI has determined age dependence of acute pulmonary responses to ozone, acute dose-response relationships for ozone in 13-day-old neonatal rats, effect of glutathione peroxidase deficiency and vitamin E deficiency on response to ozone, and effect of ozone on pulmonary function. PI has performed preliminary studies (outside of his scope of work) on the age dependence of acute pulmonary response to sidestream cigarette smoke (SS) to compare to ozone effects. The age dependence for increase in PGE_2 was not apparent with SS as with ozone.

2504065388

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

The investigators found that lactating rats showed heightened sensitivity to 1 ppm ozone compared to their suckling offspring and to age-matched virgin females, the magnitude of which was large enough to warrant continued investigation of lactating rats as a sensitive subpopulation. Rats from day 17 of gestation through day 20 of lactation were more sensitive to 1 ppm ozone than comparably aged virgin females ($p<0.05$). Peak response occured in the 13-day postpartum lactating rats. The results of analysis of LTB_4, a 5-lipoxygenase pathway product, in lung lavage fluid of neonates and adult rats exposed to 1 ppm ozone for 2 or 6 hours indicate that LTB_4 may not be important as a mediator in the ozone-induced inflammatory response as is the effect of ozone on pulmonary arachidonic metabolism via the cyclooxygenase pathway.

STATUS: September 1992

Progress is good. Airway reactivity in the rat - After exposure to 1 ppm ozone for 2 hours, adult female rats showed equal or less response to methacholine challenge compared to baseline values. Preliminary indications of experiments in which the response of trachea rings to methacholine challenge were measured are that prior in vivo exposure to ozone does not increase and may decrease responsiveness. Therefore, the rat is not sensitive to ozone-induced airway reactivity and is not a good model for the human. Work has begun on assessing the relative sensitivity of lactating and virgin female rats to inhaled endotoxin.

STATUS: March 1993

Awaiting final report.

250406538

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Gunnison A

Publications, Abstracts, and Presentations supported by CIAR

1. Gunnison AF, PA Weideman, M Sobo, KL Koenig, and LC Chen. 1992. Age-dependence of responses to acute ozone exposure in rats. Fund Appl Toxicol 18:360-369.

2. Gunnison AF, PA Weideman, and M Sobo. 1992. Enhanced inflammatory response to acute ozone exposure in rats during pregnancy and lactation. Fund Appl Toxicol. 19:607-612.

3. Gordon T, PA Weideman, and AF Gunnison. 1992. Increased pulmonary response to inhaled endotoxin in lactating rats. Fund Appl Toxicol. Submitted.

25040653390

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Building Ventilation and Smoking Policy Effects on Indoor Air Quality and Employee Comfort and Health

PI: Alan Hedge, Ph.D.
Cornell University
Department of Design & Environmental Analysis

The objectives of this work are to determine the extent to which ETS is related to the perception of comfort and health of office workers in office buildings, the extent to which different smoking policies and ventilation conditions impact on indoor air quality in office buildings, and the extent to which differences in perceived comfort and health of office workers are related to smoking policies and ventilation conditions in office buildings.

Contract No.	89-004	89-004A	89-004B
Contract Execution Date	5/19/89	1/1/91	1/1/92
Contract End Date	12/31/90	12/31/91	12/31/92
No Cost Extension	8/31/91		12/31/93
Budget	$261,419	$162,018	$138,698
Budget Amendment			
Interim report due	Quarterly		
Interim report received	8/31/89, SV, 3/12/90, 8/1/90, 12/12/90, 3/20/91, 7/11/91, 12/2/91, 7/7/92, 11/92		
Site visit (anticipated)			
Site visit (conducted)	11/13/89		
Final report due		for work through 12/92	4/93
Final report received			
Continuation approved	12/20/90	12/26/91	1/1/93

2504065391

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Contract No.	89-004C
Contract Execution Date	1/1/93
Contract End Date	12/31/93
No Cost Extension	
Budget	$78,052
Budget Amendment	
Interim report due	5/93
Interim report received	
Site visit (anticipated)	
Site visit (conducted)	
Final report due	1/94
Final report received	
Continuation approved	

STATUS: August 1991

Project is progressing on schedule. PI has completed IAQ and questionnaire surveys in proposed 9 buildings. Final survey sample will exceed 5000 workers. Return rates on questionnaire survey is in excess of 60%.

STATUS: January 1992

Associations between IAQ and employee reports of SBS symptoms were investigated for 4479 workers in 27 office buildings with 5 different smoking policies. No significant effects of smoking policy were found for levels of CO, CO_2, RSP, air temperature, relative humidity, and illumination. Significant policy effects were found for concentrations of formaldehyde, UV-PM, and nicotine, with the highest concentrations found in the "smoking restricted to areas with filtration" policy. The results show that the average concentrations of most pollutants were lowest in the "smoking prohibited" and "smoking restricted to areas with separate ventilation" policies. However, the concentrations were very low and in all buildings IAQ measures met the current ASHRAE standards for acceptable indoor air quality.

2504065392

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The results of self reports of SBS symptoms given by workers suggest that prohibiting smoking does not reduce the prevalence of SBS symptoms. Results of regression analysis show that gender, VDT use, job stress, job satisfaction, and PIAQ scores are correlated significantly to total number of SBS symptoms. Duration of exposure to workplace ETS is weakly correlated for non- and former smokers. There is no correlation between duration of total ETS exposure and prevalence of SBS symptoms. Counts of synthetic mineral fibers in office dust were significantly correlated with SBS symptoms in buildings.

STATUS: September 1992

All data analyses on the data collected on the 27 buildings and the 4,479 office workers surveyed have been completed and are in final report preparation. Five buildings from the previous sample were re-surveyed. Two of these were and still are smoking prohibited buildings, and are acting as controls. Three have changed from 'smoking restricted to workstations' to 'smoking prohibited'. Laboratory analysis and questionnaire data has been entered for comparative analyses to assess the impact of changing smoking policy on IAQ and on perceived conditions and health.
Questionnaire data from the extended survey (designed to collect psychological profiles of respondents) is almost complete for correlation analyses to assess the relationships between perceived conditions, health, and psychological variables.

STATUS: March 1993

27-building study (from abstract)

There was no effect of smoking policy on CO, CO_2, RSP, formaldehyde, relative humidity, air temperature or illumination, but there was an effect on UVPM and nicotine. Complaints of poor ventilation and thermal conditions were associated with air temperature, complaints of dry air with formaldehyde, and stale air with carbon dioxide. Neither smoking policy nor smoking status affected SBS complaints. Mental fatigue, headache, dry eyes and dry skin were associated with formaldehyde, nasal symptoms with relative humidity, and lethargy and eye complaints with illumination. Gender, hours of computer use, job stress, job satisfaction, and perceived indoor air quality also were associated with SBS complaints.

Effect of change in smoking policy, from smoking restricted to each workstation to smoking prohibited (SPCP), on IAQ and SBS:

- CO levels were slightly higher in 4 of 5 buildings in second survey.
- CO_2 levels were unaffected by change in smoking policy.
- RSP levels were consistently slightly lower in SPCP buildings.
- Formaldehyde levels were consistently lower in all buildings; no evidence that this reduction is a consequence of the change in smoking policy in the 3 smoking prohibited-unchanged policy (SPUP) buildings.
- nicotine was not detectable in SPUP buildings, but still detectable at a low level in the SPCP buildings.
- air temperatures were almost identical in all buildings in both surveys.
- relative humidity levels were unaffected by smoking policy.

2504065393

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

There is no evidence that worker's perceptions of indoor air quality were significantly improved by the change in smoking policy in the SPCP buildings.
There was no evidence of any reduction in SBS symptoms because of the change in smoking policy in the SPCP buildings.
SBS reports were significantly associated with role conflict and workload but not with role ambiguity.
Of several psychological factors, only job stress was significantly associated with SBS.

2504065394

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Publications, Abstracts, and Presentations supported by CIAR

1. Hedge A, WA Erickson, and G Rubin. 1992. Effects of personal and occupational factors on sick building syndrome reports in air conditioned offices. In: Work and well-being: Assessments and Interventions for Occupational Mental Health (Quick, JC, LR Murphy, and JJ Hurrell, Jr. eds.), Chap. 19, Washington, D.C. American Psychological Association, pp. 286-298.

2. Hedge A, WA Erickson, and G Rubin. 1991. The effects of smoking policy on IAQ and SBS complaints in 18 air-conditioned offices. Healthy Buildings-IAQ '91, ASHRAE, 151-159.

3. Hedge A. 1991. Psychosocial and environmental influences on SBS. Indoor Air Pollution, University of Tulsa, Division of Continuing Education, The Center for Environmental Research and Technology, 2-3 May, H1-H15.

4. Hedge A, WA Erickson, and G Rubin. 1991. VDT use, job stress, job satisfaction and the SBS in offices. In: Designing for Everyone (Queinnec, Y and F. Daniellou, eds.) Proceedings of the 11th Congress of the International Ergonomics Association, Vol. 1, Taylor & Francis, 713-715.

5. Hedge A, WR Erickson, and G Rubin. 1990. Building ventilation and smoking policy effects on IAQ and employee comfort and health. Indoor Air '90, Proceedings of the 5th International Conference on IAQ and Climate, Toronto, Canada. 1:739-744.

6. Hedge A. 1990. Questionnaire design guidelines for investigations of "sick" buildings. Indoor Air '90, Proceedings of the 5th International Conference on IAQ and Climate, Toronto, Canada. 1:605-610.

Hedge A. 1991. Health studies of buildings in the USA including the effects of different smoking policies on IAQ and SBS in air conditioned offices. Asia-Pacific Public Works Congress and Trade Show, Brisbane, Australia, 1-5 September.

Hedge A, WA Erickson, and G Rubin. 1991. Smoking policy, IAQ and SBS in offices. Presented at British Occupational Hygiene Society Conference, Nottingham, UK, 9-12 April.

Hedge A, WR Erickson, and G Rubin. 1990. The roles of job stress and job satisfaction in the etiology of the SBS in offices. Proceedings of the APA/NIOSH conference "Work and well-being: an agenda for the 90s", 15-17 November, Washington, DC.

Hedge A. 1990. Sick buildings, healthy buildings: Environmental psychology and workplace design. Keynote address presented at 98th Annual Convention of the American Psychological Association, Boston, 10-14 August.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Hedge A. 1992. Why do gender, job stress, job satisfaction, perceived indoor air quality and VDT use influence reports of the sick building syndrome in offices? In: Work With Display Units '92, Luczak H., AE Cakir, and G. Cakir (eds.), Technische Universitat Berlin, Institut fur Arbeitswissenschaft, A-2.

Hedge A. 1992. Sick buildings, sick terminals, sick workers-is there a link? In: Work With Display Units '92, Luczak H., AE Cakir, and G. Cakir (eds.), Technische Universitat Berlin, Institut fur Arbeitswissenschaft, I-32.

Hedge A. 1992. Occupational stress and the sick building syndrome: A survey of 4,479 office workers. Paper presented at: Stress in the 90's: A changing workforce in a changing workplace, Washington D.C. American Psychological Association/NIOSH Conference, Nov 19-22.

Hedge A. Man-made mineral fibers and the sick building syndrome in offices. Annals of Occupational Hygiene. In preparation.

Hedge A., WA Erickson, and G. Rubin (1993) Indoor air quality and sick building syndrome in 27 air-conditioned offices: the effects of five smoking policies. Paper to be presented at Building Design, Technology and Occupant Well-being in Cold and Temperate Climates, Brussels, February 17-19.

Hedge A. (1992) Indoor Air Quality and "Sick" Building Syndrome in Offices, Human Ecology Forum 20(1)2-6.

Hedge A. (1992) Does increasing the ventilation rate improve IAQ and reduce complaints? Skylines 17(1), BOMA, pp.32-33.

Hedge A. (1989) New Standard Practice for Surveying Office Occupants for Indoor Environment Effects on Health and Satisfaction. ASTM Draft Standard. November, 1989 (under revision following preliminary ASTM ballot: decribes survey method and questionnaire based on CIAR funded research).

Abstracts submitted to Indoor Air '93, Helsinki, Finland:
Hedge, Erickson, and Rubin
Effects of Restrictive Smoking Policies on IAQ and SBS: A study of 27 air-conditioned offices.

Effects of man-made mineral fibers in settled dust on SBS in air-conditioned offices.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Measurement of the Hygroscopicity of the Indoor Aerosol

PI: Phillip K. Hopke, Ph.D.
Clarkson University
Potsdam, New York

Important in the understanding of particle deposition patterns in the human lung is the growth of particles by the uptake of water vapor within the respiratory tract. This project will test a system being developed to measure the hygroscopic growth of particles and then will measure the hygroscopicity of particles from a number of specific particle sources under controlled laboratory conditions, followed by field studies.

Contract No.	92-02		
Contract Execution Date	12/10/91		
Contract End Date	12/10/92		
No Cost Extension	6/8/93		
Budget	$63,345	$64,923	$67,948
Budget Amendment			
Five month report due	5/10/92		
Five month report received	6/5/92		
Site visit (anticipated)			
Site visit (conducted)	11/10/92 (ME)		
Ten month report due	4/10/93		
Ten month report received	3/15/93		
Continuation approved			

STATUS: JANUARY, 1992

SEPTEMBER, 1992

PI requested a six month extension to the first year's grant period due to staffing arrangements. Since then, Dr. S. K. Dua, an experienced researcher in aerosols and lung deposition, has been recruited for the project from Bombay, India. Construction and testing of the Tandem Differential Mobility Analyzer (TDMA) are nearing completion and a

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

cigarette smoking machine has been obtained from the American Health Foundation in Valhalla, N.Y. PI expects to begin to make hygroscopic growth measurements shortly.

MARCH, 1993

The first step in the implementation of this program was the development and testing of the TDMA system. The TDMA has been built with a wetted wall humidifier that provides relative humidities in excess of 99%. The system permits measurements of particle size distributions from 5 nm to several hundred nanometers and allows the determination of the effects of humidification on those size distributions.

The PI has examined a series of combustion aerosols including cigarette smoke, candles, methane and propane gas burners, and incense smoke. The hygroscopic growth experiments showed that these combustion aerosol particles could grow 10%-220%, depending on their sizes and origins. In addition to the combustion aerosols, particles from 6 different pressurized aerosol products (WINDEX glass cleaner; FANTASTIK general purpose cleaner; VIDAL SASSOON hair spray; KINNEY furniture polish; BLACKFLAG house & garden insect killer; and LYSOL disinfectant spray) were studied. In these studies, it was found that the hygroscopicities of consumer product aerosols vary significantly, some behave like salt particles, some do not grow at all, and some have moderate growth. For those particles that grow, the growth ratios increase with initial size like salt particles. The curves are steep in small size range because of the Kelvin effect and flatten in large size range, although the curvatures are not as regular as those of pure compound particles.

In order to have an independent method to determine the size of a particle exposed to the humidified air, the PI is in the process of constructing an electrodynamic balance. The entire instrumentation needed for the operation of the balance is expected to be ready by April 1993 and the actual experiments will start shortly thereafter. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Li, W. and Hopke, P.K. "Initial Size Distributions and Hygroscopicity of Indoor Combustion Aerosol Particles," submitted to Aerosol Science and Technology, October, 1992.

2. Hopke, P.K., Li, W., and Dua, S.K. "Hygroscopicity of Consumer Product Aerosls," to be presented at Indoor Air '93, Helsinki, Finland, July 4-8, 1993.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The Effects of Partition Layouts and Supply Parameters on Indoor Air Quality and Ventilation Effectiveness in a Large Office

Postdoctoral Fellow: **Zheng Jiang, Ph.D.**
Centre for Building Studies
Concordia University
Montreal, Canada

The objective of this research work is to predict the airflow pattern, contaminant dispersion and thermal comfort level in a large office room, with a fixed layout of ventilation supply and exhaust, for a number of possible partition arrangements.

Fellowship Year	'91-'92	'92-'93
Start Date	July 1, 1991	July 1, 1992
End Date	June 30, 1992	June 30, 1993
Budget	$30,000	$30,000
Reports received	1/21/92	
	5/29/92	

STATUS: September, 1992

A numerical model has been developed to evaluate the impact of partition layouts on contaminant removal and ventilation effectiveness in a large partitioned office equipped by three different ventilation systems. They are (1) mixing ventilation with ceiling-mounted four-way diffuser, (2) mixing ventilation with wall jet diffuser, and (3) displacement diffuser.

With each ventilation system, a numerical optimization of the office layout is conducted by comparing several possible partition layouts in terms of the overall contaminant level in the entire office, the average contaminant concentration and average age of air in each chamber. The percentage of dissatisfied people in each chamber due to perceived air quality is taken to evaluate the removal effectiveness. With the displacement ventilation system, the bouyancy effects and the thermal comfort due to draught are investigated as well.

The results show that when a properly designed layout of partitions is used, the ventilation effectiveness in the office could be improved significantly. The source location relative to partition and ventilation openings is very important in reducing the contaminant level.

It is found that the ceiling four-way diffuser is more suitable for a partitioned office than the wall jet diffuser and the displacement diffuser. For the displacement diffuser and wall jet diffuser, it is suggested that when the exhaust opening is placed on the wall opposite to

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the supply opening, the arrangement of chambers in the central area of the office is preferable.

The present study shows that the numerical simulation is a practical and powerful tool for designers to use to optimize air distribution systems and to select a suitable layout from a number of alternatives for an existing ventilation system. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Jiang, Z. "Contaminant Control in an Office with Partitions: Part 1 - Change of Number and Size of the Partitions." Submitted to ASHRAE Transactions.

2. Jiang, Z. "Contaminant Control in an Office with Partitions: Part 2 - Comparison of Partition Arrangement for Individual Workstations." Submitted to ASHRAE Transactions.

3. Jiang, Z. and Haghighat, F. "Ventilation Effectiveness in a Partitioned Office with Displacement Ventilation." Submitted to the 5th International Jacques Cartier Conference, October 7-9, 1992, Montreal, Canada.

4. Jiang, Z., Haghighat, F. and Chen, Q. "Contaminant Control in an Office with Partitions: Part 3 - Displacement Ventilation with Buoyancy Effect." Submitted to ASHRAE Transactions.

5. Jiang, Z., Haghighat, F. and Chen, Q. "Influence of Air Supply Parameters on Air Quality in Individual Workstations." Submitted to ASHRAE Transactions.

MARCH, 1993

An investigation was conducted to study the effect of ventilation rate and partition layout on the pre-ventilation time required to allow the VOC concentration in a newly painted office to drop to an acceptable level. A displacement ventilation system, with different operating conditions, was used to remove the VOC in an office. Assuming the mass transfer coefficient to be constant, the VB emission model was improved to include the influence of non-uniform distribution on the VOC emission rate from the paints. The average VOC concentrations in the occupied zone and in each chamber were recorded hourly until the average concecntrations in the office were less than $0.0005 g/m^3$.

Results show that the time required to reduce the concentration in the occupied zone to the criterion above is dependent on the partition layout. For the same ventilation rate, the required time is approximately 4-8 hours longer when using a side layout than when using a central layout. The non-uniform concentration distribution exerts a great influence on the decay of the VOC emission rate. As the average concentrations in chambers are non-uniform, the time required for the

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average concentration in each chamber to reach the criterion is different. The time differences between chambers having the highest and lowest concentrations are about 3 to 8 hours.

Associated Manuscripts and Abstracts/Presentations

1. Jiang, Z. and Haghighat, F. "Effect of Air Diffuser and Partition Layout on the Ventilation Conditions of Workstations," accepted by Indoor Air '93, The 6th International Conference on Indoor Air Quality and Climate, July 4-8, 1993, Helsinki.

2. Jiang, Z., Haghighat, F. and Zhang, Y. "The Impact of Ventilation Rate and Partition Layout on VOC Emission Rate: Time-Dependent Contaminant Removal," submitted to The International Journal of Indoor Air Quality and Climate, March, 1993.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Chronic ETS Exposure to Developing Rats: Effects on the Lung C-Fiber System

PI: Jesse P. Joad, MD
Division of Cardiovascular Medicine
University of California, Davis

The investigators will test the hypothesis that prolonged exposure of the developing organism to ETS results in an increased sensitivity to one or more components of the bronchopulmonary C-fiber system. Exposures of rats to sidestream smoke will run from birth to 8 weeks of life. Effects to be studies are on airway obstruction, tachykinin release, tachykinin metabolizing enzymes, tachykinin receptors, and processing of C-fiber afferent input in the CNS.

Contract No.	92-05		
Contract Execution Date	6/30/92		
Contract End Date	6/29/93		
No Cost Extension	(6 months from 1/92 to 6/92 - new start)		
Budget	$130,407	$106,560	$113,385
Budget Amendment			
Five month report due	11/92		
Five month report received	11/92		
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	4/93		
Ten month report received			
Continuation approved			

STATUS: January 1992

Contracts have been sent for university signatures.

STATUS: September 1992

Contract executed.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: March 1993

Protocol changes: PI is using guinea pigs (instead of rats) and exposing them to capsaicin (instead of phenyldiguanide) from age 8 days to 6 weeks.
Preliminary results: ETS exposure (RSP=1.01 mg/m^3, CO=5.7 ppm, nicotine=541 ug/m_3) increased baseline dynamic compliance (C_{dyn}) but did not change baseline pulmonary resistance (R_L) or pulmonary artery pressure (P_{PA}). ETS exposure reduced airway reactivity to capsaicin but did not change airway reactivity to Substance P. P_{PA} reactivity to both capsaicin and Substance P was not effected by ETS exposure.
Preliminary conclusion: ETS exposure to developing guinea pigs increases C_{dyn} and alters the bronchopulmonary C-fiber system by reducing airway reactivity to capsaicin, an effect which does not involve the Substance P receptor system or the end organ.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Susceptibility to Ozone-Induced Airway Inflammation

PI: Steven R. Kleeberger, Ph.D.
Johns Hopkins University
School of Hygiene and Public Health

A unique genetic model of lung inflammation will be used to study the molecular mechanisms involved in the development of lung inflammation which may ultimately determine susceptibility to ozone-induced pulmonary inflammation.

Contract No.	90-27	90-27A	90-27B
Contract Execution Date	8/6/90	8/22/91	8/22/92
Contract End Date	8/5/91	8/21/92	8/21/93
No Cost Extension			
Budget	$133,974	$139,609	$148,809
Budget Amendment		$115,780	124,378
Five month report due	1/91	1/92	1/93
Five month report received	2/91	2/92	3/93
Site visit (anticipated)			4/20/93
Site visit (conducted)			
Ten month report due	6/91	6/92	FINAL 8/93
Ten month report received	7/91	5/92 (progress) 9/92 (budget)	
Continuation approved	8/91	9/92	

STATUS: August 1991

Budget amendment reflects appropriate reductions due to approval for funding of EPA grant proposal with overlapping scientific objectives. Project is progressing on schedule. PI has obtained evidence consistent with hypothesis that a single (autosomal recessive) gene confers susceptibility to inflammation induced by sub-acute exposures to 0.3 ppm ozone. Studies are progressing to map the Inf locus. PI has further defined the role of the cytochrome P-450 system in ozone-induced alteration of lung permeability (mouse strains, B6 and C3). Results imply that potentially injurious products of lung-oxidant interaction are formed after oxidant is removed.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

The investigators have characterized the inflammatory response to 48 hr continuous exposure to 0.3 ppm O_3 to animals of varying susceptibility. The ratios of susceptible and resistant phenotypes in these mice conform to Mendelian control of susceptibility to ozone-induced inflammation. Results of gene-mapping and co-segregation studies indicated that susceptibility to inflammatory effects of acute and sub-acute exposures is under the control of more than one gene, and that the mechanisms of susceptibility of these exposures are different. The investigators soon will publish a map assignment for the gene which controls the susceptibility to sub-acute exposure.

STATUS: September 1992

Progress is very good. Single-gene inheritance has enabled the investigators to use two specific recombinant inbred strains of mice for gene mapping and co-segregation analysis. Experiments on sub-acute ozone exposures indicate that epithelial damage (necrosis and sloughing of epithelial cells, and greater proliferation) in the nasal airways of C3 mice is significantly greater than in B6 mice, leading to the speculation that the upper airways may protect the lung from ozone's oxidative damage. Observed trends in preliminary data on characterization of anti-oxidant enzymes in B6 and C3 mice before and after exposure to ozone suggest that tocopherol (vitamin E) and retinol (vitamin A) are differentially mobilized in the mouse strains with sub-acute exposure. A new research initiative to assess the relationship between steady-state non-specific airway responsiveness and ozone-induced airway inflammation and hyperreactivity is underway.

STATUS: March 1993

HPLC techniques were used to determine concentrations of retinol (vA), retinyl palmitate (R-P), and/or tocopherol (vE) in B6 and C3 mice. Results indicate that B6 and C3 mice differ in baseline tissue levels of vA but not vE. Acute ozone exposure elicits differential tissue loss of vA and vE between strains, and may be important in determination of susceptibility to ozone-induced lung injury.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Publications, Abstracts, and Presentations supported by CIAR

1. Kleeberger SR, L-Y Zhang, and RC Levitt. 1991. Inf locus control of ozone-induced airway inflammation maps to chromosome nine in the mouse. Amer. Rev. Resp. Dis. 143:A545.

2. Kleeberger SR and L-Y Zhang. 1991. Cytochrome P-450 enzymes partially mediate acute ozone-induced change in lung permeability of genetically susceptible mice. Amer. Rev. Resp. Dis. 143:A545.

3. Kleeberger SR, MA Trush, and L-Y Zhang. 1992. Acute ozone-induced change in lung permeability of genetically susceptible and resistant mice is differentially mediated by cytochrome P-450 enzymes. (Invited presentation for the Third European Meeting of Environmental Hygiene. Dusseldorf, Germany, June 1991). In: Environmental Hygiene III. Seemayer NH and W Hadnagy (eds). Springer, Heidelberg. pp 113-116.

4. Kleeberger SR. 1991. Understanding biological variablilty in susceptibility to respiratory disease: animal models. (Invited presentation for American Thoracic Society, Anaheim, CA). Pharmacogenetics 1:114-118.

5. Kleeberger SR, RC Levitt, and L-Y Zhang. 1992. Airway inflammatory responses to 2 ppm O_3 and 0.30 ppm O_3 are controlled by different loci. Am Rev Resp Dis 145(4):A608 (Abstract).

6. Kleeberger SR, RC Levitt, and L-Y Zhang. 1992. Susceptibility to 0.30 ppm ozone-induced inflammation is genetically determined in inbred mice. Am Rev Resp Dis 145(4):A608 (Abstract).

7. Kleeberger SR, JE Seiden, L-Y Zhang, W Hadnagy, and NH Seemayer. 1992. Ozone(O_3)-induced cytogenetic effects in alveolar macrophages of differentially susceptible inbred mice. Toxicologist 12(1):69 (Abstract).

8. Kleeberger SR, RC Levitt, and L-Y Zhang. 1993. Susceptibility to ozone-induced inflammation. I. Genetic control of the response to subacute exposure. Am J Physiol 264 (Lung Cell Mol Physiol 8):L15-L20.

9. Kleeberger SR, RC Levitt, and L-Y Zhang. 1993. Susceptibility to ozone-induced inflammation. II. Separate loci control responses to acute and subacute exposures. Am J Physiol 264 (Lung Cell Mol Physiol 8):L21-L26.

10. Kleeberger SR, L-Y Zhang, C Wierenga and JR Harkema. 1993. Regional differences in airway susceptibility to subacute ozone exposure in inbred strains of mice. Amer Rev Resp Dis (abstract). To be presented May 1993.

11. Paguette NC, L-Y Zhang, W Ellis and SR Kleeberger. 1993. Ozone-induced changes in tissue tocopherol, retinol, and retinyl palmitate in differentially susceptible inbred mice. Amer Rev Resp Dis (abstract). To be presented May 1993.

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12. Disilvestre D, J Johns, SR Kleeberger and RC Levitt. 1993. Genomic sequence analysis and meiotic mapping of mouse manganese superoxide dismutase. Amer Rev Resp Dis (abstract). To be presented May 1993.

Manuscripts submitted for publication:

Zhang L-Y, RC Levitt and SR Kleeberger. Ozone-induced change in airway reactivity of inbred mice: roles of base-line reactivity and inflammation.

Paquette NC, C Tankersley, L-Y Zhang and SR Kleeberger. Repeated subacute ozone exposures in differentially susceptible inbred mice: inflammation and control of breathing.

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Adsorption of Indoor Organic Gases onto Activated Carbon Fibers

PI: **Susan M. Larson, Ph.D.**
University of Illinois at Urbana-Champaign
Department of Civil Engineering

This project will experimentally and numerically evaluate the effectiveness of activated carbon fibers (ACF) as an adsorbent to remove organic gases from indoor environments. The organic compounds of interest include acetone, formaldehyde, and toluene. These compounds are typically observed in indoor environments, and they are related to environmental tobacco smoke (ETS). Water vapor will also be studied as a competitive adsorbate that can adsorb onto ACF preferentially to the gaseous organic compounds.

Contract No.	91-03	91-03A	91-03B
Contract Execution Date	3/14/91	3/14/92	3/14/93
Contract End Date	3/14/92	3/14/93	3/14/94
No Cost Extension			
Budget $94,746	$95,813	$97,795	
Budget Amendment			
Five month report due	8/14/91	8/14/92	
Five month report received	8/14/91	8/10/92	
Site visit (anticipated)			
Site visit (conducted)	11/6/91		
Ten month report due	1/14/92	1/14/93	
Ten month report received	1/14/92	1/15/93	
Continuation approved			

STATUS: August 1991

Existing gas generation and adsorption measurement devices have been modified, recalibrated, and integrated into one system to measure the adsorption of low concentrations of individual gases onto ACF samples. Initial tests have shown that a sample of ACF-15 can adsorb 14 mg of benzene per gram of ACF in 375 hours at a concentration of 75 ppbv and 11 mg toluene/g ACF in 375 hourss at a concentration of 95 ppbv. The length

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of time needed to reach equilibrium may take from several weeks to months based on the rates of adsorption seen in the preliminary tests.

The PI has chemically modified several different types of ACF with a variety of surface treatments. The modified fibers have been examined by characterizing the physical surface properties by elemental analysis, BET surface area measurements, and by adsorption of select organic gases at saturated gas pressures. The pore size distribution of all three types of untreated fibers have been measured with the Horvath-Kawazoe or Dubinin-Astakhov methods with argon or carbon dioxide gas.

Using Mathematica, the PI has carried out preliminary calculations based on the Dubinin-Stoeckli equation for numerical modeling of single compound adsorption onto ACFs. Project is on schedule.

JANUARY, 1992

Adsorption isotherms were measured for acetone in air at concentrations of acetone between 10 ppmv and 50 ppmv with ACF samples with select specific surface areas, to experimentally quantify adsorption capacity. In contrast to adsorption behavior at saturated gas phase adsorbate concentrations, at ppmv concentrations of acetone, ACF with lower specific surface areas adsorbed more contaminant gas per unit mass of ACF than did the ACF with higher specific surface areas.

Adsorption of acetone onto ACF samples and onto a sample of granular activated carbon (GAC) as a function of time also was experimentally investigated. These kinetic data show that the adsorption rate of acetone onto the ACF samples was higher than that of acetone onto the GAC sample. Desorption of acetone from saturated ACF occured at a much lower rate than did adsorption.

Kinetic data were collected for adsorption of ppbv levels of benzene and toluene onto ACF. Due to the long time required to reach equilibrium for the ppbv concentration levels, a new experimental procedure was developed for measuring adsorption isotherms for ppbv concentrations involving a controlled environment chamber housing four smaller chambers. Each chamber will contain multiple ACF samples which will be exposed to a different contaminant gas concentration. Weight gains of the ACF samples due to adsorption of contaminant gas will be measured gravimetrically.

Numerical simulations of adsorption isotherms have been developed and show good agreement with experimental measurements. Equilibrium adsorption was modeled using the Dubinin-Stoeckli equation for acetone with ACF of three different specific surface areas. A numerical model of the adsorption kinetics (mass as a function of time) of individual VOCs onto ACF is under development. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Removal of Gaseous Organic Contaminants from Indoor Air with Activated Carbon Fibers," R.G. Fuerman, M. Cal, S.M. Larson, M.J. Rood. Conference

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proceedings for the June 1991 Annual Meeting of the Air and Waste Management Association.

2. "Removal of Gaseous Organic Contaminants from Indoor Air with Activated Carbon Fibers," R.G. Fuerman, M. Cal, S.M. Larson, M.J. Rood, October, 1991, Traverse City, the National Meeting of the American Association for Aerosol Research.

3. "Adsorption of Indoor Organic Gases onto Activated Carbon Fibers," R.G. Fuerman, Masters thesis completed December, 1991, University of Illinois at Urbana-Champaign.

4. "Comparison of the Theoretical and Experimental Results for the Adsorption of VOCs onto Activated Carbon Fibers," M.P. Cal, M.J. Rood, and S.M. Larson. Accepted for the conference proceedings for the June 1992 Annual Meeting of the Air and Waste Management Association.

5. Two manuscripts are in preparation for submittal to the journal Carbon: "Selectivity of Low Concentration Adsorption with Activated Carbon Fibers," K. Foster, R.G. Fuerman, J. Economy, S.M. Larson, M.J. Rood, and "Adsorption of ppmv Levels of Select Volatile Organic Compounds from Air with Activated Carbon Fibers," R.G. Fuerman, S.M. Larson, M.J. Rood.

SEPTEMBER, 1992

Adsorption isotherms of n-butane from approximately 50.0 ppm to 99.5% by volume in nitrogen have been completed for ACF-10, ACF-15, ACF-20, and ACF-25. Below a crossover point of approximately 5000 ppmv of n-butane, ACF with lowest specific surface area has the greatest adsorption capacity, but above appproximately 5000 ppmv of n-butane, ACF with largest specific surface area adsorbs more n-butane.

Micropore size distributions of the ACF will be measured with a newly installed instrument, an Omnisorb 100 (Coulter Corporation). The size distributions will be determined by analyzing adsorption isotherms measured with the instrument with select theoretical relationships linking adsorption isotherms to pore size distributions.

Adsorption modeling with the Dubinin-Radushkevich equation has been used to predict the amount of VOC adsorbed at equilibrium as a function of VOC concentration and ACF pore volume and pore size. The model was used to predict adsorption for three theoretical adsorbents of varying pore size and pore volume and for adsorbates varying in concentration from zero to saturation.

Packed bed adsorption tests have begun using low concentrations of VOC flowing through a packed bed of ACF to a flame ionization detector (FID) to determine the breakthrough characteristics of ACF. Consistent with experimental measurements of equilibrium adsorption, the breakthrough tests indicate that for VOCs in ppmv concentrations, ACF samples with lower specific surface areas have larger breakthrough times, indicating greater adsorption capacity. Project is on schedule.

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Publications, Presentations, and Awards

1. "Adsorption Characteristics of Trace Volatile Organic Compounds in Gas Streams onto Activated Carbon Fibers," K.L. Foster, R.G. Fuerman, J. Economy, S.M. Larson, M.J. Rood, Chemistry of Materials, accepted July, 1992.

2. "Theoretical and Experimental Results Describing the Adsorption of VOCs onto Activated Carbon Fibers," M.P. Cal, S.M. Larson, M.J. Rood, 1992. Paper 92-79.11. Conference proceedings for the June 1992 Annual Meeting of the Air and Waste Management Association.

3. "Adsorption of Volatile Organic Compounds from Gas Streams onto Activated Carbon Fibers," K.L. Foster, M.J. Rood, S.M. Larson, J. Economy. Accepted for presentation at the annual meeting of the American Association for Aerosol Research, October, 1992, San Francisco.

4. "Adsorption of Volatile Organic Compounds in Gas Streams onto Packed Beds of Activated Carbon Fibers," K.L. Foster, O.W. Graf, M.J. Rood, S.M. Larson, J. Economy. Submitted for presentation at the annual meeting of the American Association for Aerosol Research, October, 1992, San Francisco.

5. "Experimental and Modeled Results Describing the Adsorption of Acetone and Benzene onto Activated Carbon Fibers," M.P. Cal, S.M. Larson, M.J. Rood. Accepted for presentation at the annual meeting of the American Institute of Chemical Engineers, November, 1992, Miami.

6. Mark P. Cal was awarded first place in the student paper competition sponsored by Lake Michigan Section of the Air and Waste Management Association. His paper, titled "Theoretical and Experimental Results Describing the Adsorption of VOCs onto Activated Carbon Fibers," was also presented in the student poster competition at the national Air and Waste Management Association's annual meeting in June in Kansas City, where he again won first place. Mark will finish his Master's thesis on the activated carbon fiber research in October and will continue Ph.D. studies at the University of Illinois at Urbana-Champaign.

MARCH, 1993

Packed bed breakthrough results were fit with the Yoon-Nelson equation in combination with the Dubinin-Radushkevich equation showing the influence of the pore size on the breakthrough time and the ability to predict the adsorption capacity of a packed bed. Extensions of the packed bed research include constructing an apparatus to simulate a more realistic set of conditions, i.e., higher flow rates, measurement of pressure drops across the bed, and use of adsorbates such as benzene, acetone, and acetaldehyde.

An environmental chamber has been completed in which multiple samples will be exposed to ppbv concentrations of VOCs. The chamber is currently being tested and will allow for multiple data points to be obtained over the long time periods (weeks) required for the ACF to come into adsorption

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equilibrium with ppbv concentrations of VOCs. Also, characterization of new ACF samples have been completed in which the specific surface areas of the samples were measured. Project is on schedule.

Publications, Presentations, and Awards

1. "Experimental and Modeled Results Describing the Adsorption of Acetone, Benzene and Acetaldehyde onto Activated Carbon Fibers," M.P. Cal, S.M. Larson, M.J. Rood. Submitted to Environmental Progress, January, 1993.

2. "Adsorption of Volatile Organic Compounds in Gas Streams onto Packed Beds of Activated Carbon Fibers," K.L. Foster, O.W. Graf, M.J. Rood, S.M. Larson, J. Economy. Publication in preparation.

3. "Adsorption of Volatile Organic Compounds using Activated Carbon Fibers," S.M. Larson, M.P. Cal, K.L. Foster, O.W. Graf, O. Ali, M.J. Rood, J. Economy. Presented at Stanford University, Department of Civil Engineering, October, 1992, Palo Alto.

4. "Characterization of the Adsorption of Organic Compounds onto Microporous Activated Carbon Fibers," M.J. Rood, M.P. Cal, K.L. Foster, R.G. Fuerman, O.W. Graf, S.M. Larson, J. Economy. Presented at the University of Goteborg, Department of Physics, 1992, Goteborg, Sweden.

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Toxicological Interactions between the Indoor Air Pollutant NO_2 & O_3

PI: Jerold A. Last, Ph.D.
University of California, Davis
Department of Internal Medicine

The investigators will examine whether NO_2 is more damaging to the rat lung when inhaled as a mixture with ozone than when inhaled alone, and will critically evaluate the relationship between total dose delivered and the rate of delivery of NO_2 and/or ozone as lung toxicants.

Contract No.	90-20	90-20A	90-20B
Contract Execution Date	5/17/90	5/17/91	5/17/92
Contract End Date	5/16/91	5/16/92	5/16/93
No Cost Extension			5/16/94
Budget	$195,385	$200,086	$201,452
Budget Amendment			
Five month report due	10/17/90	10/91	10/92
Five month report received	10/09/90	12/91	11/92
Site visit (anticipated)			
Site visit (conducted)		5/20/91	
Ten month report due	4/91	4/92	4/93
Ten month report received	5/91	5/92	
Continuation approved	6/91	6/92	

STATUS: August 1991

Project is progressing on schedule. PI found that synergistic effect (in body weight change and total lavage protein) was elicited only when ozone and nitrogen dioxide were presented simultaneously. Other scenarios gave additive responses. PI modeled O_3 and NO_2 reaction and postulated that reactive intermediate $(N_2O_5)^3$ causes the synergistic effect. PI is planning exposure of rats to the pure compound.

STATUS: January 1992

Current results indicate that O_3 and NO_2 interact synergistically in acute exposures only at concentrations greater than found in typical indoor environments. The assay specific threshold for the most sensitive assay occurs between 0.2-0.4 ppm ozone with 3.6-7.2 ppm NO_2. Based on

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classical kinetics theory and known rate constants, the investigators predict that >95% of gas phase reaction products will be N_2O_5. The investigators have initiated the chronic exposures (90 day) to O_3 and/or NO_2 per the contract. Work is proceeding on schedule with no problems.

STATUS: September 1992

Progress is good. The investigators' results demonstrate that acute lung damage is a function of cumulative dose (CxT) for higher dose rates, i.e., 0.4, 0.6, 0.8 ppm O_3 and 7.2, 10.8, 14.4 ppm NO_2. However, when the lowest dose rate (0.2 ppm O_3 or 3.6 ppm NO_2) is used over the longest exposure duration (24 hr) to yield the same cumulative dose, a marked attenuation of pulmonary response is observed. Results of experiments with O_3-NO_2 mixtures with constant CxT demonstrate that lung damage is a function of peak concentration rather than cumulative dose.

STATUS: March 1993

PI is continuing to make good progress in performing experiments toward proposed aims. Results of chronic exposure of rats to 14.4 ppm NO_2-0.8 ppm ozone suggest that massive remodeling of the lung is occurring. Histopathology confirms that the animals have end-stage fibrotic lungs. This finding may represent the development of the first real animal model of progressive idiopathic pulmonary fibrosis.
Preliminary cell turnover data show large differences between controls, ozone or NO_2, and ozone plus NO_2.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Publications, Abstracts, and Presentations supported by CIAR

1. Gelzleichter TR, H Witschi, and JA Last. 1992. Toxicologic interactions between ozone and nitrogen dioxide: Relationship between chemical reactivity and synergistic effects. Toxicologist 12(1):229. (Abstract).

2. Gelzleichter TR, H Witschi, and JA Last. 1992. Concentration-response relationships of rat lungs to exposure to oxidant air pollutants: A critical test of Haber's law for ozone and nitrogen dioxide. Toxicol. Appl. Pharmacol. 112:73-80.

3. Gelzleichter TR, H Witschi, and JA Last. 1992. Synergistic interaction of nitrogen dioxide and ozone on rat lungs: Acute responses. Toxicol. Appl. Pharmacol. 116:1-9.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Development of Fast Atom Bombardment Mass Spectral Techniques for the Identification of Unknown Carcinogen-Nucleoside Adducts

PI: **Jackson O. Lay, Jr., Ph.D.**
University of Arkansas, Little Rock
Department of Chemistry

An analytical strategy using FAB/MS will be developed to determine molecular weights and major fragment ions of unknown carcinogen-nucleoside adducts in human samples. These methods will likely permit DNA adducts to be used as biological dosimeters of exposure to carcinogens in indoor air.

Contract No.	90-002	90-002A	90-002B
Contract Execution Date	1/22/90	6/28/91	6/28/92
Contract End Date	1/22/91	6/28/92	6/28/93
No Cost Extension	4/30/91		10/28/93
Budget	$63,120	$69,558	$76,454
Budget Amendment			
Five month report due	NA	11/28/91	3/28/93
Five month report received	NA	1/21/92	3/31/93
Site visit (anticipated)			
Site visit (conducted)	1/14/91	1/21/92	
Ten month report due	2/30/91	4/28/92	
Ten month report received	1/14/91	5/7/92	
Continuation approved			

STATUS: August 1991

The data obtained thus far suggest that the fast atom bombardment mass spectral methodology has the potential to allow detection and identification of adducts at the 1 pmole level. Significant evidence has been obtained to justify the assertion that the first two components of the analytical strategy, derivatization and constant neutral loss (CNL) scans, can be used to obtain the molecular weight of nucleoside adducts in an experiment suitable for screening mixtures of adducts. Initial studies also suggest that the BH_2^+ fragment ions of arylamine adducts give characteristic fragments in daughter ion scans that may be used as a probe

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of adduct structures. Because this strategy uses CNL scans first to identify all nucleoside adducts, and then daughter ion scans for structure elucidation, it should have great potential for application to unknown adducts and mixtures at the picomole level.

The PI will be delivering the presentation, "Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Unknown Carcinogen-nucleoside Adducts," at the International Agency for Research on Cancer Conference, which is jointly sponsored by the National Center for Toxicological Research, October 26 - November 1, 1991, in Kailua-Kona, Hawaii. In addition, the manuscript has been submitted to the Journal of the American Society for Mass Spectrometry.

JANUARY, 1992

Recent efforts have centered around improving the detection limit sufficiently (low femtomole range) that the FAB/MS method could be used in human dosimetry. The PI has investigated the use of single reaction monitoring (SRM) for the analysis of specific carcinogens (i.e., one analyte per analysis). Another MS approach, namely laser desorption/time of flight (LD/TOF) MS was also used to investigate the possibility of obtaining full scan spectra, for the analysis of unknown or multiple adducts, with femtomole sensitivity. This technique has great potential for this application because spectra are obtained based on the integration of the total signal level over time, rather than the exclusion of signal by mass filter.

The PI has demonstrated that the methods developed can be applied to in vivo samples, provided the levels of DNA modification are sufficient to allow sample sizes within their sensitivity limits to be obtained. Interferences from the biological matrix were not noted in this experiment, suggesting that the major emphasis of the future work should be directed towards continued improvements in the sensitivity.

In addition, the PI is attempting to sort out the fragmentation mechanisms giving rise to the daughter ions that were previously used for structure elucidation. The use of SRM for adduct analysis is critically dependent on the selection of the correct ion (fragmentation pathway) for adduct characterization. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Femtomole Screening and Quantification Strategies for Arylamine-modified Nucleosides by FAB/MS/MS," M.P. Chiarelli, M.S. Bryant, and J.O. Lay Jr., Analytical Biochemistry, submitted.

2. "Detection and Characterization of DNA Adducts at the Femtomole Level by Desorption Ionization Mass Spectrometry," J.O. Lay Jr., M.P. Chiarelli, and M.S. Bryant, Environmental Health Perspectives, in press.

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3. "Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Carcinogen-nucleoside Adducts," M.S. Bryant, M.P. Chiarelli, and J.O. Lay Jr., Journal of the American Society for Mass Spectrometry, in press.

SEPTEMBER, 1992

A four month no-cost extension was requested to accommodate bringing in a visiting professor to the project. Dr. Paula S. Branco will contribute to the synthesis of model compounds and the isolation of modified nucleosides from tissue DNA. She and a research assistant (an MS candidate currently enrolled at UALR in the Dept. of Electronics and Instrumentation) will assume the salary monies formerly appropriated for Dr. Chiarelli, whose salary will now come from a Veterans Administration fellowship.

The PI has worked to lower the detection limit, to the low femtomole range, so that MS analysis of modified nucleosides could be applied to applications such as human dosimetry. Two independent approaches were investigated. Experiments were undertaken to determine if single reaction monitoring (SRM) had sufficient sensitivity to be applied to analyses of specific (i.e., targeted) carcinogens. This procedure is analygous to the Constant Neutral Loss (CNL) method developed during the first year of the study, except that one modified nucleoside is measured in each experiment, albeit with much improved sensitivity compared to CNL scans. In addition, he has conducted experiments using laser desorption (LD) time-of-flight (TOF) MS, a technique potentially suitable for use in applications involving unknown adducts where SRM experiments would not be feasible.

In summary, the minimum amount of nucleoside-carcinogen adduct necessary for detection of the protonated molecule and BH_2^+ fragment ion in full-scans using TMS derivatization and FAB/MS was about 1 ng. In FAB/CNL and SRM experiments the detection limits were 500 and 10 (median value) pg, respectively. The lowest detection limit observed in fulll scans was obtained using LD with a TOF instrument. Although only a small portion of the target was irradiated, spectra were observed when samples as small as 10 pg were applied to the target. For adduct levels of 1 in 10^8 nucleosides, a detection limit of 10 pg (20 femtomoles) would make the analysis of tissue samples as small as 1 gram feasible, assuming quantitative recovery in the preliminary isolation steps. Project is on schedule, considering four month extension.

Because of the recognition the PI has gained in the course of these studies, he was asked and did submit a review article covering the mass spectrometry of DNA adducts to Mass Spectrometry Reviews.

Associated Mauuscripts and Abstracts/Presentations

Issued :
"Development of Fast Atom Bombardment Mass Spectral Methods for the Identification of Carcinogen-nucleoside Adducts," Journal of the American Society for Mass Spectrometry, 3, 360-371 (1992).

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

MARCH, 1993

In the analysis of a targeted nucleoside isolated from human DNA, the human tissue sample sizes routinely available allow only 100 ug of DNA to be isolated. Until human tissue samples having higher levels of 4-ABP modification (greater than 1 adduct per 10^7) are identified, or the detection limit is lowered, experiments involving human dosimetry based on 4-ABP-nucleoside analysis are not feasible. The PI is investigating the analysis of smaller quantities of adducts, using LD/TOF MS, in an attempt to reach the "1 in 10^8" level of modification. Until then, experiments using frozen samples of dog tissue, archived at NCTR, containing known quantities of 4-ABP are being conducted.

The PI has not made any significant progress toward the analysis of DNA adducts from coal-tar dosed animals. This is a reflection of the fact that the DNA adduct levels observed in ongoing NCTR experiments for EPRI, which were to be the source of the unknown adducts, have resulted in three orders of magnitude lower levels of DNA modification than were expected.

Work continues on the refinement of the method to increase the sensitivity, specificity and the scope of application of LD/TOF for the analysis of ultra low (less than 1 femtomole) quantities of DNA adducts.

The syntheses of a number of model diol-epoxide adducts associated with human exposure to PAHs have been completed. Sufficient quantities of material have been isolated to begin analysis using FAB, MS/MS and LD/TOF mass spectrometry. Preliminary evidence indicates that the FAB mass spectral behavior of these compounds is quite different than that observed previously with arylamines.

Recent tandem MS results on acetylated and non-acetylated adducts have provided important insights into the mechanisms of fragmentation and, hence, the structure of acetylated and non-acetylated arylamine adducts.

Associated Manuscripts and Abstracts/Presentations

1. Fu, P.P., Miller, D.W., von Tungeln, L.S., Bryant, M.S., Lay Jr., J.O., Huang, K., Jones, L. and Evans, F.E. (1991) Carcinogenesis 12, 609-616.

2. Lay Jr., J.O., Chiarelli, M.P., Bryant, M.S. and Nelson, R.W. (1993) Environ. Health Perspect. 99, 191-193.

3. Chiarelli, M.P., and Lay Jr., J.O. (1992) Mass Spectrom. Rev. 11, 447-493.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The Pulmonary Effects of ETS Exposure on Asthmatic Subjects
PI: Samuel B. Lehrer, Ph.D.
Tulane University Medical Center

The researchers will characterize pulmonary reactions to ETS and analyze the underlying mechanisms of this response. "Smoke-sensitive" and "smoke-tolerant" asthmatics as well as normal individuals will be studied to assess the specificity of ETS induced lung function changes.

Contract No.	89-0	90-11	90-11A	90-11B	90-11C
Contract Execution Date	3/17/89	4/27/90	3/8/91	3/1/92	3/1/93
Contract End Date	2/28/90	2/28/91	2/29/92	2/28/93	2/28/94
No Cost Extension					
Budget	$301,582	$270,720	$311,701	$273,561	$265,116
Budget Amendment					
Five month report due	8/91				8/93
Five month report rec'd	8/26/91				
Site visit (anticipated)					
Site visit (conducted)	8/3/89	1/11/91	1/17/92		
Report due	1/90	1/91	1/92	1/93	3/94
Report received	2/90	1/91	3/92		
Continuation approved	3/90	4/91	3/92	3/93	

STATUS: August 1991

Project is on schedule. Exposure chamber has been modified for production of gas phase smoke by HEPA filtration of sidestream smoke. Forty challenge subjects have been contacted. Thirteen have been challenged with SS-ETS. Challenge studies will continue until at least 10 reactors are identified. Reactors will be rechallenged with filtered SS-ETS. Nasal secretions will be measured by nasal lavage procedure as an extension of current study. PI is attempting to detect tobacco-specific antibody responses with immunoblotting techniques.

Co-investigator, Dr. Prem Menon, has opened a private allergy practice and is now working on this project part-time. Dr. Manuel Lopez, Chief of the Section of Allergy and Clinical Immunology at Tulane, and Dr. Jonathan Musmand have replaced Dr. Menon on this study.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

Fifty additional subjects have been challenged. Status update pending CIAR's receipt of continuation application.

STATUS: September 1992

Flourescent particulate matter (FPM) and UVPM for ETS monitoring were compared in the challenge chamber with the gravimetric method as reference. The FPM method offers greater sensitivity than the UVPM method with detection limits of 0.13 and 1.7 ug ETS per mL methanol for FPM and UVPM, respectively.

ETS Challenge:

Pulmonary Function Changes - 12 of 50 asthmatics challenged with ETS (1400 ug/m^3 TSP) were responders (drop in FEV_1 was greater than 20%). Three of these 12 had positive sham challenges and were dropped from the study. Seven responders can proceed in challenge studies as of March. Report of results of these alleged challenges is overdue.

Tobacco-specific antibody responses - 30 of the 50 subjects were skin tested with common aeroallergens, smoke extract, and two tobacco leaf extracts. Neither atopy nor skin test reactivity to any smoke or tobacco extract was significantly associated with reactivity to SS-ETS on challenge. IgE antibody responses to tobacco leaf extract were investigated by probing extract proteins with sera from SS exposed reactors and non-reactors. In one study, only one serum had weak IgE binding. In another study, strong IgE binding was detected in sera from both reactor and non-reactor groups. Combined results of antibody studies do not support an IgE-mediated response to ETS having a significant role in induced asthma.

Mediator levels - Studies of mediator levels in lavage fluids to determine the nasal and pulmonary response to the ETS challenge have begun in collaboration with the Laboratory of Clinical Investigation, Allergic Disease Section, NIAID, NIH.

STATUS: March 1993

Pulmonary function changes: About 10% of smoke-sensitive asthmatics actually demonstrated changes in pulmonary function from high level ETS exposure. The responses were not related to IgE antibody reactivity to tobacco allergens.

FPM as a marker for ETS: The FPM technique was evaluated in two private offices and in a private home. ETS levels were near the limit of detection for the UVPM method, but were an order of magnitude greater than the limit of detection for the FPM technique.

Skin test studies: Of the SS-ETS reactors tested, 6/10 did not react to any tobacco leaf or smoke extract; of the 4 skin test reactors, 2 responded to 1R4F leaf extract, 3 reacted to tobacco mix extract, and 2 to tobacco smoke extract. Results of these studies strongly support earlier observations that no basis exists for an allergic IgE-mediated asthmatic response to tobacco smoke.

Nasal lavage analysis after acute ETS exposure: Neuropeptide levels were found to be significantly affected by acute ETS exposure. The changes found in neuropeptide secretion could, in part, explain observed acute respiratory tract responses to ETS exposure.

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Gas-phase SS-ETS challenges: Results demonstrate that most SS-ETS reactors have a positive challenge response upon gas phase exposure. This study suggests that the gas phase components in SS-ETS may be affecting an irritant response.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Lehrer S

Publications, Abstracts, and Presentations supported by CIAR

1. Menon PK, RP Stankus, RJ Rando, JE Salvaggio, and SB Lehrer. 1991. Asthmatic response to passive cigarette smoke; persistence of reactivity and effect of medications. J Allergy Clin Immunol. 88:861.

2. Menon PK, RJ Rando, RP Stankus, JE Salvaggio, and SB Lehrer. 1992. Passive cigarette smoke challenge studies: Increase in bronchial hyperreactivity. J Allergy Clin Immunol. 89:560-566.

3. Rando RJ, HG Poovey, PK Menon, and SB Lehrer. Assessment of multiple markers of ETS in controlled steady-state atmospheres in a dynamic test chamber. Amer Indust Hyg Assn J. Submitted.

4. Menon PK, RJ Rando, H Poovey, JE Salvaggio, and SB Lehrer. Provocative inhalation challenge of asthmatic subjects with sidestream cigarette smoke in a dynamic test chamber. In prep.

5. Rando RJ, KT Abera, HG Poovey, and SB Lehrer. 1992. Evaluation of fluorescent particulate matter as a specific and sensitive marker of ETS. Abstract. Presented at American Industrial Hygiene Conference and Exposition, Boston, June.

6. Menon PK, RJ Rando, and SB Lehrer. 1991. Skin reactivity to tobacco leaf (TLE) and smoke extracts (TSE) in relationship to clinical tobacco smoke reactivity. Proceedings of the American Academy of Pediatrics, New Orleans.

7. Rando RJ, PK Menon, HG Poovey and SB Lehrer. 1992. Assessment of multiple markers of ETS in controlled steady-state atmospheres in a dynamic test chamber. American Industrial Hygiene Association Journal. 53:699-704.

8. Rando RJ, HG Poovey and SB Lehrer. Use of suspended fluorescent particulate matter as a marker to ETS in air. In prep.

9. Menon PK, R Rando, H Poovey and SB Lehrer. 1992. Extra pulmonary responses to sidestream ETS during ETS provocation inhalation challenges. Proceedings of the American Academy of Pediatrics.

10. Musmand JJ, M McCants, M Lopez, P Menon and SB Lehrer. Tobacco smoke allergy: A fallacy? Ann Allergy. In press.

11. Musmand JJ, M White, M Lopez, MA Kaliner and SB Lehrer. The nasal response to ETS. J Allergy Clin Immunol. In press.

12. Lehrer SB, JJ Musmand, RJ Rando, M Lopez and M McCants. 1993. Specificity of asthmatic responses to sidestream cigarette smoke challenge in a dynamic test chamber. Proceedings of the 6th International Conference on Indoor Air Quality and Climate, Helsinki, Finland, July 4-8. Submitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

13. Musmand JJ, M White, M Lopez, B Mosimann, MA Kaliner and SB Lehrer. Sidestream cigarette smoke induced perturbations of neuropeptides in the respiratory tract of asthmatics. In prep.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Indoor Aldehydes and Bronchial Hyperreactivity

PI: George D. Leikauf, Ph.D.
University of Cincinnati Medical Center
Department of Environmental Health

The researchers will determine if formaldehyde depresses or inactivates mechanisms by which it induces airway hyperreactivity. The airways are at risk from indoor formaldehyde exposure due to the high aqueous solubility and irritant properties of this compound.

Contract No.	90-010	90-010A	90-010B
Contract Execution Date	3/2/90	3/1/91	3/1/92
Contract End Date	3/2/91	3/1/92	3/1/93
No Cost Extension			4/30/93
Budget	$184,370	$164,388	$176,901
Budget Amendment			
Five month report due	NA	8/1/91	8/1/92
Five month report rec	NA	8/19/91	6/92, 9/29/92
Site visit (anticipated)			
Site visit (conducted)	12/19/90		8/10/92
Ten month report due	1/2/91	1/1/92	
Ten month report rec	1/31/91	1/27/92	
Continuation approved			

STATUS: August 1991

Examination of the influence of epithelial derived mediators on airway smooth muscle responsiveness and characterization of the effects of formaldehyde on the release of these mediators is progressing well. Following in vivo exposure of guinea pigs to selected concentrations of formaldehyde, measurements were made on 1) in vivo airway resistance, 2) in vivo airway reactivity, and 3) in vitro airway reactivity. Results indicate that total pulmonary resistance (sR_t) measured by whole-body plethysmography was markedly increased, in vivo reactivity increased, and the reactivity of the smooth muscle in vitro increased.

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Experiments involving in vitro exposure of isolated trachea followed by tests of smooth muscle responsiveness in vitro are scheduled to begin 9/91. The in vitro exposure of airway epithelial cells in culture followed by smooth muscle responsiveness in vitro will begin in early '92.

In contrast to the demonstrable effects on physiological tests, histological analysis to date has not demonstrated any changes in inflammatory cells infiltration into the lamina propria on the epithelium. Further, no changes in the number of cilia cells/mm epithelium have been observed. Thus, epithelial damage is subtle at these exposure levels. Project is substantially on schedule.

JANUARY, 1992

Having determined that the contractile response of guinea pig tracheal smooth muscle was greater after in vivo formaldehyde exposure, the investigator is now examining the specificity of this response. Previous studies have demonstrated that epithelial damage/removal increases smooth muscle sensitivity to neuropeptides to a greater extent than to histamine or cholinergic agonists. That is why the original proposal involved the study of neurokinin A and substance P. However, since they found a similar response of guinea pig trachea to both substances, and since there are more published tests conducted with substance P, the less expensive of the two, they conducted an initial series of tests with substance P.

The results of this work indicated that formaldehyde exposure produced a lowering in the cumulative dose of substance P necessary to produce half maximal contraction and potentiated the maximal response. Phosphoramidon, an inhibitor of neuropeptidase present in the airway epithelium, produced a response similar to that produced by formaldehyde, suggesting that formaldehyde induced hyperreactivity in part through epthelial damage and loss of neuropeptidase activity. Further studies are planned to examine this possibility.

The in vitro exposure work has been initiated using isolated trachea and cells in culture and exposing them to formaldehyde. This follows upon the improvement of culture methods of guinea pig tracheal epithelial cells and their growth in serum-free medium. The investigator has indicated that the methods used in the in vitro studies are giving good responses. The project is on schedule.

SEPTEMBER, 1992

In the studies exposing guinea pigs to formaldehyde for 2 h or 8 h, specific pulmonary resistance and airway reactivity (to infused acetylcholine) increased with formaldehyde exposure. After 2 h exposures, resistance was increased at concentrations equal to or greater than 10 ppm, whereas after 8 h exposure, resistance was increased at concentrations greater than or equal to 0.3 ppm. Likewise, after 8 h, reactivity was increased at concentrations greater than or equal to 0.3 ppm formaldehyde. No significant histological changes were noted in airway epithelial cells or in inflammatory cells at 0, 1, 3, 24, 48 or 96

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h after 3.4 ppm exposure for 8 hours. Tracheal rings isolated from animals exposed to 3.4 ppm x 8 h demonstrated increase maximal response (tension generated) to 10 uM acetylcholine or carbachol. Thus, formaldehyde increases airway reactivity at concentrations relevant to indoor environmental exposures and this response can be examined in vitro.

In addition to increasing cholinergic reactivity, formaldehyde exposure increases reactivity to the neuropeptide, substance P. The findings so far suggest that formaldehyde not only increases neuropeptide release but also degrades neutral endopeptidase and thereby increases the amount and half-life of neuropeptides in the airway. Currently, the PI is extending tests to include different doses of formaldehyde and to include kinetic evaluation of neutral endopeptidase.

In collaboration with Ira Richards at the University of South Florida, the PI has begun to analyze the effects of formaldehyde on human airway smooth muscle. Freshly-isolated tissue (obtained from organ donors) was exposed to formaldehyde in vitro for 3 hours. Immediately upon exposure, formaldehyde induces a transient, dose-dependent contraction. The transient character of the response is reminiscent of the transient increase in resistance observed in guinea pigs in vivo. Moreover, formaldehyde also increases cholinergic reactivity of human airway smooth muscle. Future tests will examine responsiveness to substance P and evaluate neutral endopeptidase activity in human airway tissue.

In addition, the examination of transcellular eicosanoid metabolism between human neutrophil and airway epithelial cells is continuing. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Leikauf, G.D.: Formaldehyde and Other Aldehydes. In: Environmental Toxicants: Human Exposures and Their Effects, M. Lippmann (ed.), Van Nostrand Rheinhold, New York, 1992, pp. 299-310.

2. Swiecichowski, A.L., Long, K.J., Miller, M.L. and Leikauf, G.D.: "Formaldehyde-induced Airway Hyperreactivity In Vivo and Ex Vivo in Guinea Pigs," Environ. Res., (submitted).

3. Leikauf, G.D., Swiecichowski, A.L., Rosbolt, J.P. and Richards, I.S.: "Aldehyde-induced Airway Hyperreactivity," (prepared).

4. Leikauf, G.D. and Driscoll, K.: "Cellular Approaches in Respiratory Tract Toxicology," (prepared).

5. Leikauf, G.D.: "Formaldehyde-induced Airway Hyperreactivity," presentation in Spring '92, Sopron, Hungary.

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MARCH, 1993

In the study of bronchoconstrictive effects of formaldehyde in guinea pigs in vivo and with human airway smooth muscle in vitro, formaldehyde exposures in high concentrations produce transient contractions in both experimental systems. Airway reactivity to acetylcholine was examined in guines pigs in vivo and ex vivo and in human airway tissue in vitro. In each system, formaldehyde reduced the dose of acetylcholine that induced contractions or heighten the maximal responses, indicative of airway hyperreactivity. The dose necessary to induce hyperreactivity in vivo was reduced from greater than 10 ppm to less than or equal to 1.0 ppm when exposures were extended from 2 to 8 hours. These findings suggest that formaldehyde can induce effects that last for greater than 24 hours after exposure to concentrations with environmental relevance.

The study with transcellular eicosanoid metabolism is going very well. The PI has obtained preliminary evidence indicating that human airway epithelial cells and human neutrophils produce more leukotriene B_4 when stimulated in co-culture. This finding is likely to help explain how indoor aldehyde exposure can produce inflammation, since leukotriene B_4 is a potent chemoattractant for inflammatory leukocytes. Because inflammation is linked to asthma, this finding will improve the understanding of the role of epithelial injury in airway inflammation. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Leikauf, G.D., Zhao, Q., Zhou, S., and Santrock, J.:"Ozonolysis Products of Membrane Fatty Acids Activate Eicosanoid Metabolism in Human Airway Epithelial Cells," American Journal of Physiology: Lung Cellular and Molecular Physiology, (submitted).

250H0654Z8

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Formaldehyde-Induced Activation of Airway Epithelial Cells

PI: **George D. Leikauf, Ph.D.**
University of Cincinnati Medical Center
Department of Environmental Health

Following the work on the initial project, this study will further investigate the cellular basis of formaldehyde-induced hyperreactivity in freshly-isolated human airway tissue and epithelial cells in culture. It will be determined whether formaldehyde (1) decreases airway neutral endopeptidase activity and/or alters eicosanoid biosynthesis, (2) increases chemotactic factor release, and (3) increases transcellular eicosanoid metabolism between leukocytes and airway epithelial cells.

Contract No.	93-08		
Contract Exec Date	5/1/93		
Contract End Date	5/1/94		
No Cost Extension			
Budget	$209,438	$204,199	$213,526
Budget Amendment			
Five month report due	10/1/93		
Five month report rec			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	3/1/94		
Ten month report rec			
Continuation approved			

STATUS: MARCH, 1993

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Mechanisms Involved in Induction of Allergic Inflammation by House Dust Mites

PI: **Richard J. Looney, M.D.**
University of Rochester School of Medicine
Department of Medicine

The hypothesis that the critical event leading to mite induced respiratory allergies is the outgrowth of mite specific T helper lymphocytes secreting cytokines (such as interleukin-4 (IL-4) and interleukin-5 (IL-5) that promote production of mite specific IgE antibodies and induce an influx of eosinophils into respiratory mucosa) will be investigated. Mite specific T helper cells from mite sensitive, atopic patients will be used.

Contract No.	90-33	90-33A	90-33B
Contract Execution Date	12/20/90	12/20/91	12/20/92
Contract End Date	12/20/91	12/20/92	12/20/93
No Cost Extension			
Budget	$95,949	$105,456	$107,809
Budget Amendment			
Five month report due	5/20/91	5/20/92	5/20/93
Five month report rec	6/3/91	6/2/92	
Site visit (anticipated)			
Site visit (conducted)	11/7/91		
Ten month report due	10/20/91	10/20/92	10/20/93
Ten month report rec	11/7/91	11/3/93	
Continuation approved			

STATUS: August 1991

The PI has established most of the techniques for the first year goals and has begun to gather useable data. He has obtained 7 useful (i.e., proliferated well in response to mite antigen compared to control) mite specific T cell clones. Data has been gathered on cytokine production from mite specific T cells, from freshly isolated peripheral blood mononuclear cells, and from peripheral blood mononuclear cells re-stimulated with PHA and PMA (a combination of mitogens that have been used by other

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

investigators to study cytokine production by T cell clones) after 7 days of stimulation with mite or tetanus.

Studies have been undertaken to compare the abilities of dexamethasone (a glucocorticoid) and forskolin (a material that activates adenyl cyclase resulting in elevated cAMP) to regulate the ratio of gamma-IFN to Il-4, using peripheral blood mononuclear cells stimulated with PHA and PMA. Also, modifications of mite antigen have begun by adding positively charged groups to it (cationization). Preliminary studies indicate that these will induce T cell stimulation, but it is uncertain whether these will be more potent than unmodified allergen, or even if they retain their B cell epitopes. Project is on schedule.

JANUARY, 1992

The studies on the characterization of cytokine production by mite-specific T cells have been expanded by establishing an additional 473 T cell clones from 15 different donors. Overall, the results seem to indicate that there will be a significant but modest difference in cytokine profile for mite clones compared to tetanus clones and this difference would be in the expected direction, i.e., the mite specific clones would appear to make more IL4 relative to gamma interferon than the tetanus clones. That the differences seen have not been striking is probably due to the selection of patients with either no or very mild symptoms related to house dust mite sensitivity. Studies will continue with patients with severe disease.

Work on the factors regulating the outgrowth of allergenic T helper cells has been expanded. The PI has found that forskolin, dexamethasone, IL-4 and possibly inhibitors of 5'lipoxygenase are able to modulate interferon production. The studies on bulk cultures will be extended to look at dose response curves.

Manipulation of the immune response to Der F1 by cationizing Der F1 has met with some difficulty. Unfortunately, all of the protein seemed to precipitate at point of origin in the gels. This approach has not been pursued further. Instead, the PI has purchased some B_6D_2 F1 mice. He intends to begin immunizing the animals with mite antigen bound to alum as soon as he has all the components for the mouse IgE ELISA. Project is on schedule.

SEPTEMBER, 1992

Because the differences found between mite- vs tetanus-specific T cell clones obtained from peripheral blood were small, the PI decided to look at cytokine production by T cells from respiratory mucosa. For these studies he obtained nasal polyps from 6 individuals undergoing polypectomy. All of theses donors had positive skin tests to house dust mite allergen as well as perennial rhinitis. Two of these donors had asthma and had aspirin sensitivity, i.e., aspirin precipitated attacks of asthma.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

From 1218 +/- 1633 pg/ml/million cells of gamma-interferon were produced but only 20 +/- 25 pg/ml/million cells of IL-4 were produced. Spontaneous total and mite-specific IgG, IgA, and IgE production by the mononuclear cells from these polyps resulted in a ratio of IgG:IgA:IgE equaling 7:47:1. This ratio is strikingly different than what is seen in serum. Additional studies on polyp and peripheral blood T cell clones showed large amounts of gamma-interferon produced but very little IL-4. Therefore, despite the fact that these patients were skin test positive and had a large number of eosinophils in their polyps, the cytokine profile did not suggest the activation of TH2 cells. It may be that IL-5 is the critical cytokine for inducing inflitration with eosinophils. The PI is now trying to get his samples assayed for IL-5 to see if his polyp patients are similar to intrinsic (non-allergic) asthmatics in a European study. The PI plans to look at tonsilectomy specimens and recently has been given approval to use normal nasal tissue.

The PI has begun collecting reagents for studies on the manipulation of the immune response to mite allergens. Using peptides for the T cell epitopes of tetanus toxoid and diptheria crim, he is planning to look at whether or not these peptides are good inducers of gamma-interferon production by peripheral blood mononuclear cells from immunized donors. If they are, then they may serve as useful adjuvants for inducing a TH1-like response when linked to Der F1.

The data on nasal polyps will be presented at the Otolaryngology meetings in September by an ENT resident in the PI's lab. Project is on schedule.

MARCH, 1993

Work on the characterization of cytokine production by mite-specific T cells has shown that it is imperative for investigators looking for T cell clones to look at cytokine profiles in primary cultures, since it may be that these cytokines produced early in in vitro culture influence the pattern of cytokine profile of the T cells that eventually grow out. The PI's work is the first study that has done this.

Concerning the factors regulating the outgrowth of allergenic helper T cells, the PI could not find evidence to suggest that the inflammation seen in nasal polyps is similar to that seen in allergic reactions, nor was he able to identify any antigen-specific immune response. All of the work would support the model that the cytokine profile of the TH cells might be determined by local factors in tissue. Since the major difference between a non-allergic and allergic inflammation of the tissue is a degranulation of mast cells by allergen-specific IgE in allergic inflammation, it would seem likely that this event should be very important in determining the type of T cell profile that develops in T cells that infiltrate tissue.

The PI has not given up on devising a better way to conduct immunotherapy for allergic disease. However, his results to date indicate that the regulation of cytokine production by T helper cells is much more complicated than he had originally envisioned. If local tissue factors are of paramount importance in determining the cytokine profile of T

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

cells, then simply trying to induce TH-1 type cells with immunization may not be effective. On the other hand, if IgE binding of allergen is the critical local factor that determines the cytokine profile of infiltrating T helper cells, induction of high levels of blocking antibody may be the most important effect of immunotherapy. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Cytokine Profile of Mite-specific T Cells from Skin Test Positive Donors," R.J. Looney, D. Pudiak, S.I. Rosenfeld. Submitted to the Journal of Allergy and Clinical Immunology, September, 1992.

2. "Accumulation of Gamma Interferon Producing TH1 Helper Cells in Nasal Polyps," C.H. Miller, D.R. Pudiak, F. Hatem, R.J. Looney. Presented at the American Academy of Otolaryngic Allergy Annual Meeting, Washington, D.C., September 10, 1992. Submitted to the Journal of Otolaryngology.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The Regional Deposition of ETS and its Influence on Radon Dosimetry

PI: John J. McAughey
Harwell Laboratory
Oxfordshire, England

In these studies, the deposition of ETS particles in different regions of the respiratory tract, and the effects of ETS on airborne radioactivity levels and degree of attachment will be measured. Results will be combined in a dose assessment of the effects of ETS on radon dosimetry.

Contract No.	90-29	90-29A	
Contract Execution Date	9/10/90	2/25/92	2/25/93
Contract End Date	9/09/91	2/24/93	2/24/94
No Cost Extension	6 months		
Budget	$80,400	$174,700	$81,700
Budget Amendment			
Five month report due	2/91	6/92	7/93
Five month report received	4/91	6/92	
Site visit (anticipated)			
Site visit (conducted)	4/91, 10/91		
Ten month report due	7/91	12/92	final 2/94
Ten month report received	11/91	3/93	
Continuation approved	1/92	3/93	

STATUS: August 1991

Project is about three months behind schedule. PI (J. Pritchard) left Harwell in August. Co-investigator (J. McAughey) is preparing a report to describe project status and personnel changes. As of April, no problems were anticipated regarding recruitment of volunteers for the study. All necessary radiochemical apparati were constructed and exposure system modified to accomodate oro-nasal breathing.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

Thoron source has been prepared, installed in glove box system, and attached to breathing engine. Exposure system for ETS and thoron, and computer based valving system and software for controlling and logging breathing patterns have been developed. Test atmospheres of ETS and thoron in the exposure facility have been generated and characterized by measurements of CO (10_6 ppm), tar particulate concentration (1 mg/m^3), particle number ($6x10^6$/cc), and nicotine (0.17 mg/m^3). Thoron progeny measurements indicate that thoron concentrations generated in the chamber will be adequate for the inhalation studies. The "unattached" fraction appeared at larger particle size than normally expected. Therefore, modifications to the thoron delivery system are being made to reduce the "unattached" fraction inhaled (ten fold) so that activity will not be deposited in the lung in a different region to that attached to ETS particles. Volunteer recruitment for exposures is complete.

STATUS: September 1992

Progress is satisfactory. One subject has completed all three exposure regimes (varying breathing pattern) followed by measurement of regional deposition. Four subjects have done single runs for one breathing pattern followed by measurement of regional deposition. The average half time observed for TB clearance was 9.2 h. Clearance values measured at Harwell previously by similar techniques for polystyrene particles and mainstream smoke (both of larger diameter than the surrogate ETS) were around 2 h. Increased clearance half times may be due to deposition lower in the terminal bronchioles of the smaller, non-hygroscopic secondary smoke particles.

STATUS: March 1993

Under three breathing patterns (nose, mouth, mouth-shallow, rapid) the deposition fraction differs, and in all cases are significantly greater than that reported by Hiller et al (1984) of 11+4%. The deposition fraction increases from 43% to 69% on switching from mouth to nasal breathing, but decreases to 22% when switching to a shallower more rapid mouth breathing pattern. ETS particulate matter deposits in slightly lower generations of the lung than mainstream smoke as confirmed by measured clearance half times. Results to date combined with known physicochemical differences between ETS and mainstream smoke suggest that extrapolation of exposure and dosimetric data for the two situations is not appropriate.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

McAughey JJ

Publications, Abstracts, and Presentations Supported by CIAR

McAughey JJ, A Black, AC Wells, DA Knight and JN Pritchard. 1993. The fate of nicotine on ageing of ETS in indoor environments. Abstract. To be presented at Indoor Air '93 Conference, Helsinki, Finland, July 4-8.

Strong JC, A Black, JJ McAughey and DA Knight. 1993. Dosimetry of ETS and attached thoron progeny. Abstract. To be presented at Indoor Air '93 Conference, Helsinki, Finland, July 4-8.

Strong JC, DA Knight and A Black. 1993. A novel method for the radio-labelling of the particulate phase of ETS. J Aerosol Sci. Submitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Indoor Air Quality and Energy Parameters Tested with Variable-Air-Volume / Bypass Filtration System

PI: Milton Meckler, P.E.
The Meckler Group
Encino, California

The proposed Variable-Air-Volume / Bypass Filtration System (VAV/BPFS) will be tested under controlled conditions to determine whether this concept improves substantially IAQ and energy conservation compared with the conventional VAV systems used in buildings today. Simulation IAQ models will assess the potential use of the BPFS in indoor environments such as offices. Also, the research team proposes to perform a preliminary analysis of the reduction of exposure vs. the cost of operating each of the control systems.

Contract No.	92-05	
Contract Execution Date	1/29/92	
Contract End Date	10/29/92	(Note:9 month contract)
No Cost Extension	5/31/93	
	7/15/93	

Budget	$109,380	
Budget Amendment	$120,380	($11,000 instr. repairs)
	$127,318	($6,938 additional filter)

Five month report due	6/29/92
Five month report received	6/24/92

Site visit (anticipated)	
Site visit (conducted)	12/15/92

Ten month report due	
Ten month report received	
Continuation approved	

STATUS: JANUARY, 1992

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

SEPTEMBER, 1992

IITRI built and installed the Bypass Filtration System (BPFS) and developed the study experimental design. During the process of fine tuning the chamber, instrumentation replacement and repairs necessitated the request for an additional $11,000 and a project extension through May '92. Subcontractor D. Moschandreas indicated that the project should be back on track for an observation of the system at a November site visit in Chicago.

MARCH, 1993

As originally designed, the work has progressed satisfactorily following the replacement of the collapsed condenser of the chamber. The initial results appeared promising, however, during discussions with the PIs at the site visit it was agreed that the present filter used for testing was effective in removing VOCs but was not efficient in removing particulate matter emitted from cigarette smoke. Since this inefficiency is related to the filter specs and not to the system design, it was decided to obtain a more appropriate filter and to repeat the necessary experiments. Work is progressing well, despite the difficulties with IITRI officially closing down the chamber facilities.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Injury in Gas Exchange Units Due to Low Level Nitrogen Dioxide

PI: Robert R. Mercer, Ph.D.
Duke University Medical Center
Department of Medicine

The researchers will study phenomena involved in the progression of chronic low level exposures to airborne pollutants and will provide techniques for the isolation of specific sites within the lung which are most likely to demonstrate changes at low levels of exposure.

Contract No.	90-22	90-22A	90-22B
Contract Execution Date	6/5/90	7/1/91	7/1/92
Contract End Date	6/5/91	6/30/92	6/30/93
No Cost Extension	to 6/30/91		
Budget	$202,159	$156,889	$162,749
Budget Amendment			
Five month report due	11/5/90	12/91	11/92
Five month report received	12/01/90	1/92	
Site visit (anticipated)			
Site visit (conducted)	5/8/91		
Ten month report due	4/5/91	5/92	final 6/93
Ten month report received	5/30/91	5/92	
Continuation approved	7/1/91	6/92	

STATUS: August 1991

Project is on schedule. PI has developed more sensitive methods to detect injury and repair of connective tissue fibers in the lungs, and has described the dosimetry model for reactive gas uptake in different gas exchange units in the lung.

STATUS: January 1992

Structural modeling for reactive gas dosimetry is complete. The determined reaction parameters for NO_2 uptake in airways and alveolar regions are being used in simulations of NO_2 uptake in rat lungs. The results of rat exposures to 3 ppm NO_2 with 9 ppm spikes demonstrate

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

significant alterations in interstitial and epithelial compartments at this dose. Predicted dose for the individual ventilatory units correlates strongly with response of epithelium and interstitium of the proximal alveolar region in these high dose exposed rats. Statistical analysis of connective tissue elements in alveolar wall and tip of alveolar septa forming alveoli from this high dose exposed group in underway. Serial section of production, reconstruction, and EM morphometry are complete and half complete for 1.5/3.0 ppm NO_2 and 0.1/0.3 ppm NO_2 groups, respectively.

STATUS: September 1992

Progress is very good. Results of NO_2 exposures indicate significant structural heterogeneity of the lungs (airways branching patterns, number and volume of ventilatory units on any specific airway) between animals. This has been put forth as one of the mechanisms producing significant variations observed in injury by inhaled pollutants. In dosimetry studies, predicted NO_2 uptake based on structural modeling of individual ventilatory units is significantly correlated with alveolar epithelial hypertrophy (AEH) at 3.0/9.0 ppm and 0.5/1.5 ppm NO_2. Compared to results from a similar study with ozone, NO_2 is 5 times less toxic in terms of AEH than ozone in the proximal alveolar region and has a more uniform injury pattern in the ventilatory unit. In morphometry studies, acute exposures to nitrogen dioxide results in alveolar septal hypertrophy with no significant alteration in the connective tissue fibers on lung parenchyma. Alveolar macrophage accumulation is correlated with alveolar septal hypertrophy.

STATUS: March 1993

PI is conducting final stages of data analysis and preparation of final report.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Mercer RR

Publications, Abstracts, and Presentations supported by CIAR

1. Mercer RR, S Anjilvel, FJ Miller, and JD Crapo. 1991. Inhomogeneity of ventilatory unit volume and its effects on reactive gas uptake. J Appl Physiol 70(5):2193-2205.

2. Presentation of 1. above at NIH workshop on environmental lung disease, May 1991.

3. Mercer RR and JD Crapo. 1991. Structural changes in elastin fibers following elastase administration in hamsters. J Appl Physiol 72:1473-1479.

4. Mercer RR, GC McCauley, and S Anjilvel. 1991. Cylindrical approximation of biologic structures. In prep for IEEE Trans on BME.

5. Environmental Criteria and Assessment Office, US EPA, Aug 14, 1991. Workshop on Identification of Ventilation Rate and Respiratory Surface Area for Inhalation RfC Methodology. Invited participant.

6. Office of Technology Assessment, US Congress, Sept 30, 1991. Workshop on Noncancer Health Threats to the Lung. Invited participant.

7. Mercer RR, ML Russell and JD Crapo. 1991. Alveolar septal structure in different species. J Appl Physiol. Submitted.

8. Clean Air Scientific Advisory Committee (CASAC), US EPA, Apr 27-28, 1992. Review of the draft National Ambient Air Quality Standards for Nitrogen Oxides. Consultant.

9. Pinkerton KE, RR Mercer, CG Plopper and JD Crapo. 1992. Distribution of injury and microdosimetry of ozone in the ventilatory units of the rat. J Appl Physiol. In press.

10. Mercer RR and JD Crapo. 1992. Three dimensional analysis of lung structure and its application to pulmonary dosimetry models. In: Toxicology of the Lungs, Gardner DE, JD Crapo, and EJ Massaro (eds.), Raven Press. In press.

11. Miller FJ, RR Mercer and JD Crapo. 1992. Modeling of lower respiratory tract structure in animals and man: Dosimetry and clinical implications. Aerosol Sci and Tech. Submitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Indoor Biological Agents: Exposures and Responses in Allergy and Asthma

PI: **Mary Kay O'Rourke, Ph.D.**
University of Arizona College of Medicine
Division of Respiratory Sciences

Building on an established population of 800 individuals representing 300 families which have been defined for purposes of studies of indoor air pollution supported by EPA, this study will take indoor air samples for pollens and other allergens and antigens to be identified by immunologic tests and compare them with respiratory symptomatology determined by questionnaire, illness, and respiratory dysfunction.

Contract No.	90-003	90-003A	90-003B	90-003C
Contract Exec Date	1/29/90	1/9/91	1/9/92	1/9/93
Contract End Date	1/29/91	1/9/92	1/9/93	1/9/94
No Cost Extension				
Budget	$148,437	$181,287	$191,021	$161,402
Budget Amendment				
Five month report due	6/29/90	6/9/91	6/9/92	6/9/93
Five month report rec	6/22/90	6/7/91	7/8/92	
Site visit (anticipated)				4/29-30/93
Site visit (conducted)	11/2/90		3/13/92	
Ten month report due	11/29/90	11/9/91	11/9/92	11/9/93
Ten month report rec	11/27/90	12/16/91	12/31/92	
Continuation approved				

STATUS: August 1991

Pollen and mold data collected during the full year of 1988 have been analyzed. The seasonal distribution of samples collected is consistent with those previously published. The study comparing air-conditioned homes versus evaporative-cooled homes is showing that mold values are appreciably higher in the latter during the summer and early fall months. As the cooling season ends, spore concentrations return to similar magnitudes.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The PI has found and verified the presence of significant numbers of house dust mites in Tucson. Evidence of Blatta (cockroach) is rare. The most common mite species found in samples is Dermatophagoides farinae; although a few specimens of D. pteronyssinus have been found. The investigation has shown all growth stages of the mites. The first batch of antigen samples (ragweed, Bermuda grass, insect, house dust mite and one mold taxon) obtained from both indoor and outdoor air has been sent to the Mayo Clinic for analysis.

Supplemental subject medical history, blood draws and complete skin testing of the 800 allergic subjects of the study are progressing well. Currently, over 400 subjects have been skin tested. The new skin test data are being entered into the data base and blood samples are being selected for IgE analysis to begin this year. Daily diary data already collected are currently being coded and entered into the data base. Overall, all aspects of the project are on schedule.

JANUARY, 1992

New collection and slide counting procedures were developed to meet the requirements by the QA officer, following the move of Jim Quackenboss to the EPA. (A visit to EPA-Las Vegas Dec. 3-5 resulted in a working arrangement between the PI and the EPA exposure analysis team for analysis of the time/activity diary data from the project to their mutual benefit. This expertise will greatly enhance the project without any additional cost.)

Seasonal and diurnal variability of indoor pollen and mold concentrations has been assessed in the field study in the two test houses. Data has been counted through the spring of 1991. The first data batches are currently being entered into the newly developed data bases, using a Dbase IV format.

The PI is preparing a manuscript of house dust mite analysis in Tucson. Results indicated that isolated mattress samples contain the highest concentration of house dust mites. Overall, mattresses and furniture contain fewer mites than floor samples. Numerous floor samples both in the main room and the bedroom contain mite concentrations exceeding 200 mites per gram of house dust.

The first batch of antigen samples has been sent to the Mayo Clinic for analysis with the results being somewhat troubling. Additional work will be performed to sort out the discrepancies.

On the human health investigations, over 500 subjects have been skin tested, 992 blood samples have been drawn, and 755 IgE samples have been processed. An analysis to determine whether time of year of blood draw influences the IgE concentrations found in the blood has been undertaken. Also, the relationship between health status (including skin test reactivity) and symptom reports is being investigated among normals, allergics and bronchial responsives under conditions of increasing pollen concentration using relative risk values. The development of an exposure model for individuals based on the amount of time spent in the home

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indoors is being facilitated by the above mentioned intereaction with personnel at EPA-Las Vegas. Project is on schedule.

Book Chapters Submitted for Publicaton

1. "The Importance of Environmental Allergens in the Development of Chronic and Allergic Obstructive Lung Diseases," M.K. O'Rourke and M.D. Lebowitz, in Environmental Respiratory Diseases, eds. S.L. Demeter, E. Cordasco, and C. Zenz.

2. "Medical Palynology," M.K. O'Rourke, to Vaughn Bryant, Playnological Laboratory, Texas A & M University, College Station, Texas.

SEPTEMBER, 1992

Regarding the determination of pollen, mold spore and airborne antigen concentrations in and around houses, graphic evidence demonstrates that less pollen is found indoors regardless of the taxon involved. Frequency of indoor pollen concentration varies seasonally in response to outdoor concentrations. This variance may be greater in seasons with moderate temperatures (i.e., early spring and fall). Currently, the PI is performing principle component analysis on these values to determine the importance of seasonality and determine which taxa respond in like fashion. Spore data are being related to fungal colony data to ascertain their relationship. Next, the PI will examine the relationship between mold colonies, spore and health effects.

In the comparative study of air-conditioned and evaporative-cooled homes, mold concentrations during the summer and fall of 1990 have been examined. Mold values are appreciably higher in the evaporatively cooled home during the summer and early fall months. As the cooling season ends, spore concentrations return to similar magnitudes in each home.

Collections of house dust mites in the homes have shown that isolated mattress samples contain the highest concentration of house dust mites. Overall, mattresses and furniture contain fewer mites than floor samples. Numerous floor samples both in the main room and the bedroom contain mite concentrations exceeding 200 mites per gram of house dust. Samples collected during the winter generally have greater mite concentrations actively reproducing (eggs are visible within the bodies of females). Seasonal patterns illustrate the declining mite concentrations in February, March and April. Mite populations increase with cooler use through the fall. Greatest concentrations are found during the winter when temperature and humidity values are most favorable for mite reproduction. Winter has the greatest number of immature mites.

Immuno-assay work on antigen conentrations from indoor and outdoor air for ragweed, Bermuda grass, insect, house dust mite and 1 mold taxon has been fraught with difficulties. Possible problems include something being wrong with the seum for assay, Tucson air being incredibly free of antigen, or the antigen assay system not being adequate for low continuous

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

exposures. Split samples are being shared with other investigators to resolve these difficulties. The PI will also attempt the blot technique which may prove more sensitive than the elution technique for detecting low level continuous indoor exposure.

The PI has begun to develop an exposure model for individuals based on the amount of time spent in the home indoors vs. elsewhere. Aside from the immuno-assay work, the project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Meeting of the American Academy of Allergy and Immunology, March, 1992, Orlando, Florida.

2. Meeting of the Eighth Palynological Congress, September, 1992, Aix en Province, France.

3. Prepared and submitted manuscript on the prevalence of housedust mites in Tucson.

4. Manuscript relating household characteristics to mite concentrations over a 2 year period, in preparation for Medical Entomology.

MARCH, 1993

Data collection on the relationship between indoor and outdoor pollen and mold concentrations for 1990-1991 continued through 1992. These samples are undergoing additional analysis for atmospheric antigen evaluation of Bermuda grass.

In the field study in test houses, the PI has examined mold concentrations during summer and fall of 1990- Dec. 1991. All samples are counted from the first home; 75% of the samples are counted from the second home. All data should be completed shortly, along with temperature and humidity values.

In the human health studies, supplemental subject medical history, blood draws and complete skin testing of the 800 subjects of the study remains underway. The PI is now current in data entry, validation and cleaning of all health and diary data. Work has begun on the peak flow data and its relationship to environmental measurements. Based on these data, the PI is developing an exposure model for individuals based on the amount of time spent in the home indoors vs. elsewhere. The PI has evidence (textbook example) correlating health effects with indoor pollen concentrations. Additionally, the mold data also looks promising. Project is on schedule.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Associated Manuscripts and Abstracts/Presentations

1. Lebowitz, M.D., O'Rourke, M.K., Paoletti, P., Sears, M.R. and Burrows, B. 1993. Airway responsiveness related to skin test reactivity. American Academy of Allergy and Immunology. Chicago, March 1993.

2. O'Rourke, M.K. and Lebowitz, M.D. 1993. The contribution of indoor pollen to total exposure: Four models. American Academy of Allergy and Immunology. Chicago, March 1993.

3. O'Rourke, M.K., Fiorentino, L., Clark, D., Ladd, M., Rogan, S., Carpenter, J., Gray, D., McKinley, L. and Sorensen, E. 1993. Building materials and importance of house dust mite exposure in the Sonoran Desert. Indoor Air '93. Helsinki, July 1993.

4. O'Rourke, M.K., Van de Water, P.K., Hjelmroos, M.K., Bernardo, M.C., Boyer-Pfersdorf, P. and Lebowitz, M.D. 1993. Indoor pollen and mold exposure among residents of an urban arid environment. Indoor Air '93. Helsinki, July 1993.

5. Stetzenbach, L.M., O'Rourke, M.K., Meldrum, J. and Boyer-Pfersdorf, P. 1993. The relationship between mold spores and colony counts as representatives of airborne fungi. Indoor Air '93. Helsinki, July 1993.

6. Stetzenbach, L.M., O'Rourke, M.K., Meldrum, J. and Boyer-Pfersdorf, P. 1993. Fungal colony and spore counts from homes in the southwest. Journal of Applied Microbiology.

7. O'Rourke, M.K., Moore, C.L. and Arlian, L.G. Factors affecting house dust mite prevalence in an arid environment. Medical Entomology.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Does ETS Promote Arteriosclerosis or Act as a Co-Atherogen?

PI: Arthur Penn, Ph.D.
NYU Medical Center
Department of Environmental Medicine

The objective of the proposed study is to determine whether chronic inhalation of ETS leads to accelerated arteriosclerotic plaque development. The researchers will determine if exposure of cockerels to ETS components results in activation of dominant transforming genes.

Contract No.	90-008	90-008A	90-008B
Contract Execution Date	2/26/90	4/1/91	2/28/92
Contract End Date	2/26/91	3/31/92	2/27/93
No Cost Extension	COST EXTENSION TO 12/31/93		$181,213
Budget	$168,186	$182,041	$174,570
Budget Amendment	1) additional $18,358 for smoke generator 2) 12/90 additional $2800 for nicotine analysis		
Five month report due	9/90	7/91	7/92
Five month report received	10/1/90	----	9/92
Site visit (anticipated)			
Site visit (conducted)	6/26/90		
Ten month report due	3/91	1/92	3/93
Ten month report received	2/18/91	1/92	1/93
Continuation approved	4/11/91	1/92	1/93

STATUS: August 1991

Project is progressing on schedule. PI has completed 60 day sidestream smoke (SS) inhalation study (TPM = 8 mg/m^3) with cockerels. Microanalysis of plaque formations was completed last month. Cockerels pre-treated with DMBA or DMSO and exposed to SS showed no significant differences in degree and size of plaques compared to pre-treated controls. PI is planning a 90-day, 6 hr/day exposure of cockerels to the same TPM level SS as above.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

The experiment - Six exposure groups, including air controls were given a single injection or five bi-weekly injections of DMBA (PAH carcinogen) or DMSO (solvent), and exposed to sidestream smoke (RSP = 9 mg/m^3) for 2 hr/day from 24-36 weeks of age. None of the treatments had any effect on body weights. None of the treatments had any effect on serum cholesterol levels. The percentage range of aortic segments in each group having measurable plaque compared favorably with values for spontaneous plaques in birds of this age. Relative plaque intensities (RPIs) were not high in any of the groups (15-39%) and none of the treatments were effective at eliciting increases in RPIs. These results indicate that exposure to sidestream smoke under the stated conditions does not play a major role in the intermediate stage of plaque development in this model.
To test the effect in early stages of plaque development, cockerels are being exposed to the same level of SS from 8-24 weeks of age for 6 hr/day, 5 days/wk. 30 animals are in the SS exposure groups and 15 in the air controls.

STATUS: September 1992

Sub-chronic inhalation study is complete. Plaque incidence was not affected by the exposures. Plaque size was significantly increased in the SS-exposed animals.

PI will submit a 1 year non-competitive continuation application at the end of this year to perform the sub-chronic inhalation study at a relevant, typical ETS level found indoors (about one order of magnitude lower TSP than the original study.)

STATUS: March 1993

PI will determine plaque indices for cockerels exposed 6 hr/day, 5 days/wk, 16 weeks (6-22 weeks of age) to two levels of SS - 1200 and 600 ug/m^3 RSP, as part of an intensive dose-response study of daily 6 hr exposures. Work is underway on the 1200 ug/m^3 RSP exposure level.

2504065448

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Penn A

Publications, Abstracts, and Presentations supported by CIAR

1. Penn A and CA Snyder. 1992. Inhalation of sidestream cigarette smoke accelerates development of arteriosclerotic plaques. Science. Submitted. Presented at 1993 annual meeting of the Society of Toxicology, March.

2504060449

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Effects of ETS on Prenatal and Perinatal Lung Development

PI: Kent E. Pinkerton, Ph.D.
University of California, Davis
Department of Veterinary Anatomy

The investigators will determine whether or not exposure to ETS adversely effects lung development in rats. The three major phases of lung development through embryogenesis to the attainment of a mature lung by three or four months of age will be assessed.

Contract No.	90-006	90-006A	90-006B
Contract Execution Date	2/23/90	1/1/91	1/22/92
Contract End Date	2/23/91	12/31/91	12/31/92
No Cost Extension	start date after ETS wkshp	5/1/91	3/31/93
Budget	$200,859	$164,539	$171,261
Budget Amendment		$5,320 carryover of equip funds from year 1	
Five month report due		5/91	5/92
Five month report received		5/91 (SV)	6/92
Site visit (anticipated)			
Site visit (conducted)	7/16/90, 11/5/90, 5/20/91		
Ten month report due	11/90	10/91	final 4/93
Ten month report received	10/24/90	12/91	1/93
Continuation approved	1/1/91	12/91	new 4/1/93

STATUS: August 1991

Project is on schedule and progressing well. 100-day exposure of rats, age birth to 100 days, to sidestream smoke will be completed 9/12/91. At day 7, 14, 21, 50, and 100, cellular kinetics, DNA incorporation, immunocytochemistry, and lung and liver P-450 levels are investigated. Results through day 50 show no body or lung weight differences between exposed and controls. A four-fold induction of P-450 was observed in 50 day old exposed rats. Investigators have been successful in measuring plasma nicotine metabolites to get an estimate of dose to the animals.

2504065450

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

Improvements to SS smoke generation system - A cigarette handling and lighting device was constructed to automatically load, light, and smoke 1R4F cigarettes using FTC mainstream conditions. A second smoking system was installed to be used simultaneously with the first but with each's smoking cycle staggered to promote greater consistency of exposure concentrations.
Biomarkers of exposure - Animals housed in wire cages or in open-top plastic cages with wood chip bedding material were simultaneously exposed to SS for 6 and 12 hours. No differences in blood cotinine levels for animals housed under either condition were found. With progressive exposure to SS, plasma nicotine levels averaged 10 ng/ml regardless of exposure length. Maximal plasma cotinine levels (100 ng/ml) were attained after 3 to 5 days of intermittent exposure to SS.
Results of measurement of the relative activity of isozymes 1A1 and 2B in rat lungs indicate that SS has a marked effect on developmental expression of CP450 in the postnatal lung. CP450 1A1 is significantly augmented in neonatal rat lungs from 7 to 21 days of age by exposure to SS and continued exposure to 100 days is associated with persistent elevation.

STATUS: September 1992

Progress is consistently very good.
In utero exposures to ETS - Exposure conditions: Pregnant SD rats from gestational days 2-21 exposed; 6 hours/day, 5 days/wk; RSP (1 mg/m^3), nicotine (350 ug/m^3), CO (6 ppm); gestational days 18 and 21 and postnatal day 1 examined. Significant decreases were noted in body weight at gestation day 21 and postnatal day 1. The cell labelling index for fetal airways demonstrated an age-dependent decrease, but no alteration due to ETS exposure. The labelling index of parenchymal cells had a significant ETS effect at gestational day 18.
Postnatal exposures to ETS - rat pups exposed postnatal days 2-100; examined at 7, 14, 21, 50, and 100 days. Exposure to SS was associated with a significant elevation in isozyme IA1 activity at each time up to 3 times higher than controls. Isozyme IIB activity was unchanged from controls.
Effects of acute vs chronic ETS exposure on cytochrome P450 isozyme activity - Alterations in IA1 and IIB activity occur quickly with exposure to SS (IA1 increases, IIB decreases). Lungs are unable to adapt to long term exposure by returning enzyme activity levels to control levels. A significant depression of isozyme IIB activity was observed in female rats but not in male rats for chronic exposures.

STATUS: March 1993

Progress is good. Project is on schedule. Awaiting final report.

2504065451

Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Publications, Abstracts, and Presentations supported by CIAR

1. Teague SV, K Pinkerton, RA Jenkins, and JH Moneyhun. 1991. ETS exposure system for whole body and nose only exposure of rodents. 1991 American Conference of Governmental and Industrial Hygienists, American Industrial Hygiene Association, Salt Lake City, UT, 18-24 May, p 6.

2. Cardoso WV, L Edwards, KE Pinkerton, CM Ji, R Philpot, CG Plopper. 1991. Immunocytochemical detection of cytochrome P-450 monooxygenases in the neonatal rat lung. Am Rev Resp Dis 143:A92.

Gebremichael A, D Morin, A Chang, S Teague, CG Plopper, AR Buckpitt, KE Pinkerton. 1992. ETS, lung development, and cytochrome P-450 activity in the neonatal rat. Abstract submitted to the 1992 American Thoracic Society Meeting.

Gebremichael A, CG Plopper, AR Buckpitt, KE Pinkerton. 1993. Development of pulmonary cytochrome P450 isoenzymes: Protein expression, activity and response to ETS in postnatal rats. Abstract. Society of Toxicology 1993 Annual Meeting.

Bric JM, KE Pinkerton and JP Joad. 1993. Chronic sidestream smoke effects on airway and pulmonary artery reactivity to serotonin in developing rats. Abstract. American Academy of Allergy and Immunology 1993 Annual Meeting.

In preparation:

2. Cardosa WV, KE Pinkerton, C Ji, RM Philpot, WM Thurlbeck and CG Plopper. Developmental expression of cytochrome P-450 monooxygenase system in rat airways.

3. Cardosa WV, L Stewart, KE Pinkerton, C Ji, GER Hook, G Singh, SL Katyal, WM Thurlbeck and CG Plopper. Comparison of clara cell secretory product expression during bronchiolar epithelial differentiation in the rabbit and rat.

4. Teague SV, KE Pinkerton, RA Jenkins and JH Moneyhun. A sidestream tobacco smoke generation and exposure system for ETS studies. To be submitted to Inhalation Toxicology.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Effects of Indoor Air Contaminants on Prenatal and Perinatal Lung Development

PI: Kent E. Pinkerton, Ph.D.
University of California, Davis

The investigators will determine dose response effects of in utero and postnatal exposure to ETS on prenatal and perinatal lungs for cell kinetics and tissue characteristics of the developing airways and parenchyma, the levels of cytochrome P450 isozyme activity in the lungs and liver, the distribution of cytochrome P450 isozymes localized immunocytochemically in the lungs, and the cytodifferentiation of nonciliated bronchiolar epithelial (Clara) cells and alveolar type II cells. These studies will serve as critical biomarkers of the sensitivity and specificity of developing lungs to ETS at relevant indoor exposure levels.

Contract No.	93-09		
Contract Execution Date	4/1/93		
Contract End Date	3/31/94		
No Cost Extension			
Budget	$221,843	$189,470	$198,884
Budget Amendment			
Five month report due	8/93		
Five month report received			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	1/94		
Ten month report received			
Continuation approved			

STATUS: March 1993

Contract fully executed 3/26/93.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Pulmonary Reactive Uptake of Inhaled Toxic Contaminants

PI: **Edward M. Postlethwait, Ph.D.**
University of Texas Medical Branch
Pulmonary Division

The proposed project is designed to characterize and compare across species (including man) the kinetics of interaction and the predominant substrates involved during the pulmonary airspace absorption of NO_2 and O_3 with the goal of establishing a model for evaluating relative dosimetry. The researchers will delineate the absorption determinants of NO_2 and O_3 within the intact, isolated lung, followed by the determination of the extent to which uptake is localized to within the epithelial lining fluid (ELF).

Contract No.	90-23	90-23A	90-23B
Contract Execution Date	7/1/90	7/1/91 (fax 6/24/91)	7/1/92
Contract End Date	7/1/91	7/1/92	7/1/93
No Cost Extension			
Budget	$126,158	$119,788	$131,306
Budget Amendment			
Five month report due	12/1/90	12/1/91	12/1/92
Five month report rec	1/24/91	12/26/91	12/15/92
Site visit (anticipated)			4/28/93
Site visit (conducted)	3/15/91		
Ten month report due	5/1/91	5/1/92	
Ten month report rec	6/6/91	6/1/92	
Continuation approved			

STATUS: August 1991

Several studies related to nitrogen dioxide reactive uptake by the pulmonary airspace surface were completed. A comparison between bulk phase exposures and "thin films" has been undertaken both for determining mechanisms of toxicity and to further validate the use of isolated epithelial lining fluid (ELF) as an investigational model. The data support the concept that NO_2 reactive absorption is limited to near the

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gas/liquid interface. The kinetic evaluations of the exposed cellular membranes are still in the initial stages.

Data from another series of studies imply that the primary substrates involved in NO_2 reactive absorption are of small molecular weight (less than 1000). Consequently, the PI has begun to explore the relative reactivity of small molecular weight solutes which occur in meaningful concentrations within the ELF. Steady-state exposures of both single and mixed substrates will be studied to determine whether the overall rate of NO_2 absorption is accurately predicted by the first order expression.

The PI has developed a new isolated lung preparation which utilizes a closed exposure system in addition to subatmospheric ventilation. Reactive uptake of nitrogen dioxide within rebreathing lungs is a first order process and displays rate saturation similar to isolated ELF. Also, studies have begun in isolated lungs investigating the effects of vascular perfusion, inspired concentration, and temperature on O_3 uptake. The approximately three-fold increased uptake coefficient has necessitated the development of the chilled lung, which should be operational in a couple of weeks.

Comparative animal studies will begin shortly, using bronchoalveolar lavage (BAL) from rabbits and mice , followed by dogs and sheep. Project is on schedule.

JANUARY, 1992

Work on the further characterization of NO_2 reactive absorption in both intact, ventilating lungs and in isolated, aqueous biological systems has continued. Results indicate that NO_2 absorption is localized to near-surface sites and that the kinetic absorption characteristics of intact lungs and isolated aqueous systems are similar, validating the design of correlating relative dosimetry in freshly harvested epithelial lining fluid (ELF). A recent study has demonstrated that alteration of airspace surface reactants profoundly affects NO_2 absorption by the intact lung. This is the first clear example that composition of airspace reactant pools directly alters dosimetry of an inhaled reactive toxicant. Preparations are being made to perform the multispecies comparative study of NO_2 reactive absorption by airspace surface fluids.

The PI has initiated studies into the mechanisms of O_3 absorption by the pulmonary epithelium and by isolated pulmonary epithelial lining fluid (ELF) and found that O_3 uptake is also mediated via a reaction-dependent component. Methodologies and approaches will follow the NO_2 reactive dosimetry work. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E. M., Langford, S. D., and Bidani, A. Transfer of NO_2 through pulmonary epithelial lining fluid. Toxicol. Appl. Pharmacol. 109:464-471, 1991.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

2. Postlethwait, E. M., Langford, S. D., and Bidani, A. Interfacial transfer kinetics of NO_2 into pulmonary epithelial lining fluid. J. Appl. Physiol. 71(4):1502-1510, 1991.

3. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of airspace interfacial transfer of inhaled NO_2 in rebreathing isolated lungs. J. Appl. Physiol. In preparation.

4. Postlethwait, E. M. and Bidani, A. Determinants of inhaled NO_2 transfer across the pulmonary airspace interface. Presented abstract to a NHLBI/NIEHS workshop on "Environmental Lung Disease," Rockville, MD, May 29-30, 1991. (A published proceeding is expected.)

5. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of NO_2 interfacial transfer into pulmonary epithelial lining fluid. (Abstract) Toxicologist 11(1):106, 1991. (Presented at the Society of Toxicology meeting, Dallas, TX, Feb., 1991.)

6. Postlethwait, E. M., Langford, S. D., and Bidani, A. Penetration of NO_2 through "thin films" of pulmonary epithelial lining fluid. (Abstract) Am. Rev. Respir. Disease 143(4):A700, 1991. (Presented at the American Thoracic Society meeting, Anaheim, CA, May, 1991.)

7. Postlethwait, E. M., Langford, S. D., and Bidani, A. Kinetics of NO_2 uptake in rebreathing isolated lungs. (Abstract) Am. Rev. Respir. Disease 143(4):A700, 1991. (Presented at the American Thoracic Society meeting, Anaheim, CA, May, 1991.)

8. Postlethwait, E.M., Langford, S.D., and Bidani, A. Kinetics of NO_2 airspace absorption in isolated rat lungs. Submitted to: J. Appl. Physiol. 12/91

9. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A., Relative NO_2 reactivity of pulmonary epithelial lining fluid reactants. Toxicol. Appl. Pharmacol. In preparation.

10. Postlethwait, E.M., Langford, S.D., and Bidani, A. Ozone reaction-mediated absorption in isolated rat lungs. Amer. Rev. Respir. Dis. In preparation.

11. Postlethwait, E.M., et al. Reaction-dependent O_3 absorption in isolated rat lungs. (Abstract) The Toxicologist. In press.

12. Postlethwait, E.M., et al. Ozone reactive absorption in isolated rat lungs. (Abstract) Amer. Rev. Respir. Dis. In press.

13. Postlethwait, E.M., et al. Ozone reactive absorption in isolated pulmonary epithelial lining fluid. (Abstract) Amer. Rev. Respir. Dis. In press.

14. Postlethwait, E.M., et al. The effect of surfactant release on NO_2 reactive uptake in isolated rat lungs. (Abstract) Amer. Rev. Respir. Dis. In press.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

SEPTEMBER, 1992

In continued progress toward the evaluation of the comparative airspace surface dosimetry of inhaled reactive gases, the PI's most recent efforts have involved completing the initial characterization of ozone uptake under quasi-steady-state exposure conditions. He has also continued his studies on the effects of in situ airspace surface conditions on NO_2 reactive uptake in isolated lungs. This is an important area of investigation since it uniquely demonstrates that situations which potentially alter conditions at the gas/liquid interface (i.e., exercise, prior exposure, existing lung disease) have the capacity to substantially alter airspace surface dosimetry.

The study which characterizes the NO_2 relative reactivity of potential reactants which are found in the epithelial lining fluid has been completed. The results of this study are of interest in terms of the most reacive and prevalent substrates (which also have relevance to other aspects of pulmonary toxicology) and lead the PI to believe that interfacial conditions within the alveolar space relative to the conducting airways may play an important role in determining local dosimetry and in the genesis of the site-specific pathology which occurs with reactive gas exposure. In addition, the PI has initiated the comparative species studies and, as a result, is preparing for the human component of the proposed work. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Mixed phase reaction kinetics between pulmonary epithelial lining fluid constituents and gas phase NO_2. Toxicol. Appl. Pharmacol. In preparation.

2. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Inhaled O_3 is cleared from pulmonary airspaces by reactive absorption. Am. Rev. Respir. Dis. In preparation.

3. Postlethwait, E.M., Langford, S.D., and Bidani, A. Reaction-dependent O_3 absorption in isolated rat lungs. The Toxicologist 12(1):231, 1992. (Presented at the Society of Toxicology meeting, Seattle, WA, February, 1992.)

4. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. The effect of surfactant release on NO_2 reactive uptake in isolated rat lungs. Am. Rev. Respir. Dis. 145(4):A98, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

5. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. Ozone reactive absorption in isolated rat lungs. Am. Rev. Respir. Dis. 145(4):A98, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

6. Postlethwait, E.M., Langford, S.D., and Bidani, A. Ozone reactive

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

absorption in isolated pulmonary epithelial lining fluid. Am. Rev. Respir. Dis. 145(4):A97, 1992. (Presented at the American Thoracic Society meeting, Miami, FL, May, 1992.)

7. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. The effects of aqueous interfacial and gas phase reactants on reactive absorption of inhaled pollutant gases. Annual Conference on Biomedical Engineering Research, Houston, TX, March, 1992.

MARCH, 1993

The data suggest that the pulmonary airspace absorption of inhaled NO_2 and O_3 are rate-limited, in part, by chemical reactions between the toxicants and constituents of the surface lining layer. The presence of solute reactants is a critical requirement for rapid absorption since in the absence of solute reactants, gas phase disappearance rates are relatively insignificant.

NO_2 interfacial transfer follows fixed-order kinetics (first-order) under specified conditions where the initial gas phase concentrations are less than 10 ppm. As such, NO_2 uptake can be mathematically described and extrapolated down to very low (environmentally relevant) concentrations where inspired concentrations by isolated lungs function as a surrogate for tracheal concentrations.

Isolated lung studies have proved extremely valuable for delineating the specific effects of individual parameters which influence the inspired dose rate (i.e., inspired concentrations of O_3 and NO_2, tidal volume (V_t), and ventilation frequency (f)). In addition, the effects of airspace surface area (altered via functional residual capacity (FRC) volumes) have also been determined. Results suggest that, under fixed conditions of inspired concentration, f, and FRC, uptake of both NO_2 and O_3 is linearly related to V_t.

There are clear species-specific differences in NO_2 reactive absorption rates by isolated ELF. The NO_2 effective rate constants (for gas phase removal) display a rank-order which is similar to the rank-order for oxidant susceptibility suggested by other authors. Direct correlation between species-specific, toxicant-specific reactive absorption rates and tissue damage/susceptibility remains to be demonstrated. Project is on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Postlethwait, E.M., Langford, S.D., and Bidani, A. 1992. Kinetics of NO_2 air space absorption in isolated rat lungs. J. Appl. Physiol. 73(5):1939-1945.

2. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. 1992. Reactive absorption mediates the intrapulmonary gas phase clearance of inhaled O_3. Am. J. Respir. Cell Mol. Biol. Submitted.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

3. Postlethwait, E.M., Langford, S.D., Jacobson, L.M., and Bidani, A. 1992. Mixed-phase reaction kinetics of gas phase NO_2 absorption by pulmonary epithelial lining fluid constituents. Tox. Appl. Pharmacol. In preparation.

4. Jacobson, L.M., and Postlethwait, E.M. 1992. Multispecies comparison of NO_2 reactive uptake by pulmonary epithelial lining fluid. Gulf Coast Society of Toxicology, Annual Meeting. ABSTRACT.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Metabolic Epidemiology of Nicotine Exposure in Nonsmokers
PI: John P. Richie, Jr., Ph.D.
American Health Foundation

The researchers will develop and validate immunochemical methods for the determination of nicotine metabolites including nicotine, cotinine, and trans 3'-hydroxycotinine to enable the conduct of large scale and relevant epidemiological studies in ETS exposure and uptake.

Contract No.	90-21	90-21A	90-21B
Contract Execution Date	6/4/90	12/26/91	
Contract End Date	6/4/91	12/25/92	
No Cost Extension	6 mos.		
Budget	$109,012	$108,212	$ 69,448
Budget Amendment			
Five month report due	12/90	5/92	5/93
Five month report received	2/91		
Site visit (anticipated)			
Site visit (conducted)	2/14/91	1/7/92	
Ten month report due	4/91	10/92	FINAL 12/93
Ten month report received	9/91	9/92	
Continuation approved	9/91	9/92	

STATUS: August 1991

Project is about 4 months behind schedule, but is progressing well at this point. PI is only 10% committed at American Health Foundation now and project underwent some slippage during the transition. CIAR has experienced administrative problems with AHF business office (i.e., CIAR has not received any invoices to date) which presently are being ameliorated. Per co-investigator J. Ritchie, a progress report and continuation application is forthcoming within a couple of weeks. Investigators are continuing work on development of polyclonal antibodies specific for nicotine metabolites. Monoclonal antibody was not sensitive enough. They are working on alternative approaches to assays for measuring nicotine metabolites: affinity chromatography to isolate the hydroxycotinine specific antibodies from crossreactive antibodies to cotinine, and HPLC with electrochemical detection to measure metabolites.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

STATUS: January 1992

Further work with monoclonal antibody approach was unsuccessful. From the results of fusions, antibody producing hybridoma cells are obtained, but they are unstable and do not continue to produce. The investigators are developing polyclonal antibodies for 3'-hydroxycotinine in rabbits. While characterizing an existing polyclonal antibody for cotinine, they found a 40% cross reactivity of this antibody with 3'-trans hydroxycotinine. The rabbit antibody recognizes also cotinine and hydroxycotinine conjugates. The investigators have modified an HPLC method developed for plasma nicotine to use dual electrode amperometric detection and have demonstrated its capability to resolve and detect nicotine, cotinine, and hydroxycotinine in urine.

STATUS: September 1992

Progress is satisfactory. Monoclonal antibodies approach was terminated. The investigators designed a new ELISA which quantifies hydroxycotinine in urine at 5 ng/mL. HPLC assay with amperometric detection was terminated because sensitivity for nicotine metabolites in urine from passively exposed individuals is too low. The investigators demonstrated increased sensitivity for the metabolites with coulometric detection, are defining optimal working conditions for their analysis and that of glucuronide conjugates, and will use this method to validate immunoassay techniques. For initial controlled ETS exposure studies to determine steady state levels of urinary nicotine metabolites after chronic heavy exposure and profile differences among smokers, ex-smokers, and passive smokers, 20 subjects have been recruited and exposed to date.

STATUS: March 1993

PI was contacted for an interim report. Status update pending receipt of the report.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

The Structural Basis for Irritant Effects of Indoor Air Pollutants

PI: Herbert S. Rosenkranz, Ph.D.
University of Pittsburgh

The investigators will use a Structure Activity expert system (CASE) to establish the structural basis for the action of sensory irritants occurring in the indoor air environment. Structural determinants for the effect will be determined and compared with those known for other endpoints. Results of this study may make it possible to predict potential activity of untested molecules and yield insight into mechanisms of action.

Contract No.	93-01
Contract Execution Date	1/1/93
Contract End Date	12/31/93
No Cost Extension	

Budget	$73,613
Budget Amendment	

Five month report due	5/93
Five month report received	

Site visit (anticipated)	
Site visit (conducted)	

Ten month report due	10/93
Ten month report received	
Continuation approved	

STATUS: March 1993

Contract fully executed 1/2//93

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Experimental Dosimetry of NO_2 using Short-Lived Radioisotopes

PI: Michael L. Russell, MD
Duke University Medical Center
Department of Medicine

Using oxygen-15-labeled NO_2 as a dosimetry tracer, the investigators will test the hypothesis that a significant alveolar region dose gradient exists causing the proximal region to absorb substantially more NO_2 than the distal region, and that the nasopharynx acts as a major determinate of alveolar NO_2 uptake. Intraspecies comparisons in rats and interspecies comparisons between mice, hamsters, rats, and guinea pigs will be examined for NO_2 deposition differences. The investigation will provide an experimentally-based analysis of NO_2 dosimetry throughout the respiratory tract.

Contract No.	92-01	92-01A	
Contract Execution Date	1/1/92	1/1/93	
Contract End Date	12/31/92	12/31/93	
No Cost Extension			
Budget	$118,713	$122,754	$127,929
Budget Amendment			
Five month report due	5/92	5/92	
Five month report received	9/92		
Site visit (anticipated)	5/93		
Site visit (conducted)			
Ten month report due	11/92	11/93	
Ten month report received	11/92		
Continuation approved	12/92		

STATUS: January 1992

Contract fully executed.

STATUS: September 1992

Project is on schedule. Progress is good.
Tracheal Elution of $N^{15}OO$ - Experiments on the diffusibility of $N^{15}OO$ in the trachea of SD rats demonstrated that the $N^{15}OO$ reaction products elute from the trachea in a bi-exponential manner. Release ratios for

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

amounts and half lives of the products suggest that either the reaction products of $N^{15}OO$ are of similar diffusivity but contained in two different physical compartments, or that there are two major categories of reaction products with different diffusivities. To eliminate hematogenous redistribution of reaction products, exposures were performed on freshly killed rats mechanically ventilated via tracheostomy (different tidal volumes). While dosimetry models predict tidal volume effects, no statistically significant differences were observed between the radioactivity retained in each of the different lung lobes. Gas exposure via tracheostomy may have introduced disproportionately more turbulent flow within the trachea at the higher tidal volume and caused more $N^{15}OO$ deposition.

A cryogenic purification system for batch processing $N^{15}OO$ was designed as is currently under construction.

STATUS: March 1993

PI has altered time table as a result of recent findings. Since NO_2 products undergo rapid hematogenous redistribution, the measured tracer distribution from a live animal exposure is different from the actual uptake distribution. Interspecies comparison of nasopharyngeal scrubbing efficiency was delayed until this second year and has been underway for a short time. The ventilatory parameter study is slated for this year rather than the airway/alveolar autoradiography study which will be performed next year. Results of cryogenic purification will appear in upcoming progress report.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Russell M

Publications, Abstracts, and Presentations supported by CIAR

1. Russell ML, JL Need, RR Mercer, FJ Miller and JD Crapo. 1992. Ventilatory parameter effects on uptake of ^{15}O-labeled NO_2 in rats. Am Rev Resp Dis 145:A92 (Abstract).

2. Miller FJ, JH Overton, JS Kimbell and ML Russell. 1992. Regional respiratory tract absorption of inhaled reactive gases. In: Toxicology of the Lung, Crapo JD, DE Gardner and RO McClellan (eds.). In press.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Investigations of Ozone Reactive Chemistry in Indoor Environments

P. Barry Ryan, Ph.D.
Harvard School of Public Health

Scope of Work: To develop modeling systems for ozone in indoor environments. The investigators will establish the importance of the contribution of chemical reactivity to human exposures in indoor environments through the use of data on ozone deposition velocities with indoor materials in chamber studies, and evaluation of pollutant concentrations in residences.

Contract No.	90-31	90-31A	90-31B
Contract Execution Date	10/10/90	9/30/91	11/4/92
Contract End Date	10/09/91	9/29/92	11/3/93
No Cost Extension			
Budget	$112,896	$104,118	$111,191
Budget Amendment		$126,627	$124,485
Five month report due	3/91	2/92	3/93
Five month report received	3/13/91	----	
Site visit (anticipated)			
Site visit (conducted)		7/8/92	
Ten month report due	8/91	8/92	final 12/93
Ten month report received	9/91	10/92	
Continuation approved	9/30/91	11/92	

STATUS: August 1991

PI's 10-month report is forthcoming within two weeks per telephone conversation. Project is on schedule. Computer networking among PI's lab, home, and university system has been accomplished. A preliminary compartmental model is running on the Sun workstation. PI is gaining experience in Macintosh system development.

STATUS: January 1992

Ozone deposition studies - Results of trials with latex paint coated glass test sections suggest that painted surfaces are reactive towards ozone. An initial high deposition fraction was observed and suggests that some mechanism involving drying paint or surface saturation controls the ozone

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loss rate. A long-term stable deposition rate suggests another mechanism. The pattern on second exposure is an initial lower deposition (30-40%) followed by a more precipitous decline and leveling off to a value similar to that seen at the end of the first exposure.

STATUS: September 1992

PI has been delinquent in reporting progress over the past year, and had little to add on his progress and results at last site visit in July. He is attempting to submit continuation application by early October.

STATUS: March 1993

Ozone deposition is related to ozone concentration, relative (or absolute) humidity, and the presence of VOCs on surfaces, and simple kinetics determines the complex behavior of ozone on surfaces.

-Changing ozone concentration does not affect the fraction deposited.
-Ozone deposition is linearly associated with relative and aboslute humidity. For paper wallpaper, the effect is less pronounced but still evident.
-Attempts to regenerate surfaces using heptene and styrene were unsuccessful.
-Paper wallpaper displayed no ability, under any experimental conditions, to react with ozone.
-Experiments with vinyl wallpaper showed little effect of relative humidity but surface could be regenerated by heating. This suggests "bake-out" of organic material from interior of wallpaper.
-RH effects dominate latex paint but there is evidence of long-term VOC effect.
-VOC effect dominates vinyl wallpaper deposition.
-Both RH and VOC effects may be operative for paper wallpaper but overall deposition is very low.
-Results of preliminary organic acid experiments on latex paint test sections suggest that the principal secondary acid produced is acetic acid.

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Inflammatory Responses after Indoor Exposure to Airborne Glucan and Endotoxin

PI: Ragnar Rylander, M.D.
University of Gothenburg
Sweden

The investigators will perform an epidemiological study on populations in sick buildings in which the extent of "sick building" symptoms will be evaluated and related to the amount of airborne endotoxin and glucan. Results may explain the origin of symptoms reported and open up a means to control the quality of indoor air.

Contract No.	90-25	90-25A	90-25B
Contract Execution Date	7/9/90	9/2/91	9/2/92
Contract End Date	7/8/91	9/1/92	9/1/93
No Cost Extension	9/1/91		
Budget	$102,756	$145,824	$125,000
Budget Amendment			
Five month report due	12/90	1/92	1/93
Five month report received	3/91	1/92	3/93
Site visit (anticipated)			10/92
Site visit (conducted)	4/91, 10/91, 7/92		
Ten month report due	5/91	6/92	final 9/93
Ten month report received	8/91	8/92	
Continuation approved	8/15/91	yes	

STATUS: August 1991

Project is on schedule. PI continued investigations on association between the extent of symptoms in buildings and amount of airborne glucan and endotoxin. Studies were conducted in office buildings, day care centers, and schools in Sweden. PI has demonstrated an association with glucan in several buildings.

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STATUS: January 1992

Sundsvall school studies data are being analyzed. Harryda (daycare centers) study is ongoing. Dust measurements, questionnaires, and bronchial reactivity measurements are being analyzed. Challenge studies have commenced. To assess experimental design, persons with SBS were exposed to known low levels of glucan, endotoxin or saline in the first study.

STATUS: September 1992

Preliminary conclusions of the Harryda study are that headache and mucus membrane irritation are significantly elevated in buildings where glucan is found compared to control buildings. Dose-response relationships between B-1,3-glucan levels and eye and throat irritation, dry cough, and itching skin were found in four buildings in which these symptoms were prevalent compared to a control building. Results of the first series of laboratory exposure studies demonstrate that exposure to glucan causes an increase in the extent of headache and that endotoxin causes increased stuffy nose symptoms.

STATUS: March 1993

The method to analyze glucan from airborne indoor dust samples is established with continuing cooperation of Japanese scientists.
Data analysis of laboratory challenge experiments comprising measurement of pulmonary function and airway reactivity as well as the registration of symptoms with questionnaires (for 24 subjects) is underway.
Data analysis of field studies comprising these measurements and exposures to airborne endotoxin and glucan in all localities is underway.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Rylander R

Publications, Abstracts, and Presentations supported by CIAR

1. Rylander R, K Persson, H Goto, K Yuasa and S Tanaka. 1992. Airborne B-1,3 glucan may be related to symptoms in sick buildings. Indoor Environment 1:263-267.

2. Rylander R and K Persson. 1991. Airborne B-1,3 glucans in sick buildings. ATS Abstract. Am Rev Resp Dis. 143:A89.

3. Rylander R and K Persson. Glucan and symptoms in Hult school 1990-91. Dep Env Med Report. March, 1991.

4. Rylander R and H Goto. Organic Dust Committee report, April, 1991. First glucan inhalation toxicity workshop, October, 1990.

5. Rylander R, Persson K, Goto H and Yuasa K. 1991. Sick building symptoms and levels of airborne glucan. In Jacobs RR, Wakelyn PJ and Domelsmith LN (eds). National Cotton Council of America, Memphis, TN, pp 236-238.

6. Rylander R. (1992) Recent experiences on effects of endotoxin and B-1,3 glucan in indoor air. Presented at XVI Cotton Dust Research Conference, Nashville, TN, Jan 9-10.

7. Rylander R and Y Peterson. 1992. Recent experiences on effects of endotoxin and B-1,3 glucan in indoor air. In: Domelsmith LN, RR Jacobs, and PJ Wakelyn (eds.), 16th Cotton Dust Research Conference, National Cotton Council, Memphis, TN, pp 288-289.

8. Rylander R. (1993) A perspective on indoor air microbiological contamination. Presented at Conference on Building Design, Technology and Occupant Well-being in Temperate Climates, Brussels, Belgium, Feb 17-19.

9. Rylander R. (1993) Experimental exposures to (1 3)-B-D-glucan. Presented at Conference on Building Design, Technology and Occupant Well-being in Temperate Climates, Brussels, Belgium, Feb 17-19.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Improved Control Strategies for Effective Ventilation with Variable Air Volume Systems

PI: Harry J. Sauer, Jr., Ph.D.
University of Missouri-Rolla

The investigators will expand on the existing ASHRAE 590-RP methodology to develop the necessary tools for properly sizing and controlling the components in VAV systems for effective ventilation and associated indoor air quality while minimizing energy usage. Results will provide the design engineer with guidance in selecting the optimal sizes and types of fans, dampers, VAV boxes, and ducts for maintaining required air quantities, proper building pressures, and minimum energy consumption.

Contract No.	93-03		
Contract Execution Date	1/1/93		
Contract End Date	12/31/93		
No Cost Extension			
Budget	$51,348	$61,387	$53,150
Budget Amendment			
Five month report due	5/93		
Five month report received			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	10/93		
Ten month report received			
Continuation approved			

STATUS: March 1993

Contract fully executed 3/12/93

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Evaluation of Effectiveness of Portable Indoor Air Cleaning Systems

PI: **Richard L. Shaughnessy, Ph.D.**
University of Tulsa
Center for Environmental Research and Technology

This project will evaluate the effectiveness of selected console-type portable air cleaners by measuring the clean air delivery rate (CADR) in removal of the following parameters: dust particulate matter, tobacco smoke, pollen, viable and total fungal spores, and gaseous contaminants (specifically carbon monoxide, nitrogen dioxide, nicotine and formaldehyde). Chamber studies will be conducted in accordance with a modified version of the Association of Home Appliance Manufacturers (AHAM) test procedures and will be followed by sensory perception studies.

Contract No.	90-26		
Contract Execution Date	7/26/90	Work Start Date	9/1/90
Contract End Date	1/31/92	(Note: 17 month contract)	
No Cost Extension	3/15/92		

Budget	$181,406
Budget Amendment	

Five month report due	2/1/91
Five month report received	2/4/91

Site visit (anticipated)	
Site visit (conducted)	5/14/90 (preliminary visit) 8/16/91

Ten month report due	7/1/91
Ten month report received	8/14/91
Final report due	3/15/92
Final report received	11/2/92

STATUS: August 1991

The following contaminants have been studied with respect to individual air cleaner removal: formaldehyde, dust, tobacco smoke particulate, and vapor-phase tobacco smoke constituents (nicotine and vinyl pyridine). In addition, ozone measurements have been taken to monitor ozone buildup

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within the chamber as a function of specific air cleaner operation. Work is in progress on the removal of total spores and pollen, to be followed by viable fungal spores. Also, two air cleaners have been placed in a home and office situation for the extended use study.

With respect to contaminant removal, the data reveal poor effectiveness in air cleaner performance on formaldehyde removal. Air cleaners without sorbent had no effect on gaseous contaminant removal. The clean air delivery rates (CADRs) for tobacco smoke (particulate) removal showed a broad variance depending on particular units. In general, HEPA and electrostatic units were most effective in the removal of particulates.

A technical paper on "The Use of Ozone Generators for the Control of Indoor Air Contaminants in an Occupied Environment" will be presented September 6, 1991 at the ASHRAE IAQ '91 Healthy Buildings Conference in Washington, D.C. Project is on schedule.

JANUARY, 1992

The above presentation was made at the ASHRAE Conference in Washington. Laboratory studies and data evaluations for the project are being completed. We await the submission of the final report.

SEPTEMBER, 1992

E. Levetin presented microbiological data at the Meeting of the American Academy of Allergy and Immunology in March '92 in Orlando, Florida. Sensory data evaluation set project timetable back. We await the submission of the final report.

MARCH, 1993

The primary objective of this study was to test portable indoor air cleaning technologies as to their individual effectiveness in removing dust particulates, tobacco smoke particulate and vapor phase constituents (nicotine and vinyl pyridine), viable and total fungal spores, pollen, and gaseous contaminants (carbon monoxide, nitrogen dioxide, and formaldehyde), within a test chamber per Association of Home Appliance Manufacturers (AHAM) specs.

Three brands of portable air cleaning systems with HEPA filters, three with electrostatic precipitators (EP), two with electret filters (EF), two with ionizers (ION), one containing both EF and ION, and two ozone generators (OZ) were tested. Many of the systems incorporated some degree of sorbent within the filtration configuration. Experiments were conducted individually to discern the air cleaners' effectiveness at specific contaminant removal. Normal decay curves were plotted for each contaminant to enable calculation of Clean Air Delivery Rates (CADR's) and system efficiencies. Cleaners utilizing electrostatic precipitators were the most efficient with respect to particulates (smoke, dust, spores, pollen), closely followed by HEPA and electret filter systems. Ion and

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ozone systems were least effective in reducing the particulate contaminants. Only systems which included sufficient sorbent materials (i.e., activated carbon or potassium permanganate, (with respect to formaldehyde)) proved to be marginally effective at reducing concentrations of gaseous contaminants (nitrogen dioxide, formaldehyde, vinyl pyridine) within the chamber. The air cleaners were least effective at removing carbon monoxide and nicotine.

The testing protocol (modified AHAM standards) for evaluation of the air cleaning systems concentrated only on the initial performance of the system. Two of the filter technologies (HEPA and EP) that proved to be the most effective at removing tobacco smoke particulate in chamber experiments were placed in typical home and office environments to study changes in effectiveness with use. Both systems displayed significant reductions in CADR's after 800 hours of operation in the respective environments.

Two panels composed of five people each participated in sensory testing to determine panel responses to three sets of conditions: (1) tobacco smoke with air cleaner in operation, (2) smoke with no air cleaner in operation, and (3) no smoke, no air cleaner in operation. The sensory testing was conducted to discern potential correlation between human perceptive response and measured air cleaner performance (with respect to tobacco smoke removal). The results of the sensory data analysis indicated that an electret filter (EF) loaded with carbon sorbent received the best ratings across the dimensions of odor strength, nasal irritation, eye irritation, and overall air acceptability. A HEPA system was the only other air cleaner producing statistically significant results on overall air acceptability.

Associated Manuscripts and Abstracts/Presentations

1. Shaughnessy, R.J., Levetin, E., and Sublette, K. "Effectiveness of Portable Indoor Air Cleaners in Particulate and Gaseous Contaminant Removal," to be presented at Indoor Air '93, Helsinki, Finland, July 4-8, 1993.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Genotoxicity of Epoxide-Induced 3-Hydroxyalkyl Uracil

PI: Jerome J. Solomon, Ph.D.
New York University Medical Center
Department of Environmental Medicine

The investigators will test the hypothesis that 3-hydroxyalkyl uracil is the critical premutagenic lesion produced by aliphatic epoxides in vivo. The results will address the mechanisms of mutagenesis and cancer induction by alkenes and will permit an evaluation of the suitability of 3-hydroxyalkyl uracil adducts in DNA as markers of exposure to, and genotoxic risk from, alkenes.

Contract No.	90-12	90-12A	90-12B
Contract Execution Date	6/12/90	6/17/91	6/17/92
Contract End Date	6/30/91	6/16/92	6/16/93
No Cost Extension			12/31/94
Budget	$237,749	$248,160	$241,944
Budget Amendment			
Five month report due	11/90	11/91	12/92
Five month report received	12/10/90	12/91	12/92
Site visit (anticipated)			
Site visit (conducted)	6/26/90		
Ten month report due	4/91	5/92	5/93
Ten month report received	5/6/91	5/11/92	
Continuation approved	6/17/91	6/92	

STATUS: August 1991

Project is on schedule. PI has progressed on the mechanism of hydrolytic deamination of the propylene oxide adduct, 3-hydroxyalkyl-dCyd. The final step of his suggested mechanism is base-catalyzed ring opening to form 3-hydroxyalkyl-dUrd. PI has progressed extensively on determining the DNA adducts which form after in vitro reaction of ethylene oxide with calf thymus DNA. In vivo exposures to propylene oxide have been delayed because of difficulties experienced by the chemical supplier and PI in synthesizing tritiated PO with sufficient specific activity. Development of a DNA repair assay to study the repair of 3-hydroxyalkyl-dUrd lesions by DNA glycosylases is complete and operational in PI's lab.

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STATUS: January 1992

DNA adducts in vitro - Alkylation at N-3 of dCyd by EO under physiological conditions results in rapid hydrolytic deamination of 3-HE-dCyd to 3-HE-dUrd mechanistically involving the hydroxyl group on the alkyl side chain which forms after epoxide alkylation. Hydrolysis experiments to determine in vitro half-life for hydrolytic deamination of 3-hydroxyalkyl cytosine adducts and to measure the pattern and persistence of DNA adducts after in vivo exposure to epoxides and olefin precursors are nearly complete.
DNA adducts in vivo - Preliminary results of persistence studies with PO show that the binding of tritiated PO to nasal cavity DNA persists with a half life of 2.3 days. Clearance of PO DNA adducts from trachea or lung is very slow.
Mutagenesis of single-stranded M13 DNA by PO - All 68 sequenced independent PO-induced mutants in M13/C141 phage DNA show sequence changes at either (or both) of the first two Cs in the target codon (pro,CCC) which result in an amino acid substitution at this site. There are significant differences in the spectrum of mutations observed after transfection of PO-treated single-stranded DNA into E. coli host cells with different DNA repair backgrounds. Relative survival and mutagenesis of PO-treated DNA experiments show that some form of mutagenic damage is repaired by uracil glycosylase which is active in wild type cells but not in ung$^-$ cells.
DNA replication - Studies suggest that alkylation of the central hydrogen bonding site (N-3) of thymidine in DNA is biologically significant and may contribute to the cytotoxic, mutagenic and carcinaogenic processes by alkylating agents.
Site-specific mutagenesis studies and DNA repair studies of 3-hydroxyalkyl-dURD are underway.

STATUS: September 1992

Progress is very good. PI is consistently productive.
In vitro mutagenesis and DNA repair - PO forms adducts at dCyd residues which rapidly deaminate to give 3-HP-dUrd residues. PO is toxic to E. Coli and toxicity is greater in cells which lack either uracil glycosylase activity or nucleotide excision repair (UvrA$^-$). PO can induce mutations at C-residues. Therefore, 3-HP-dUrd lesions are likely to be mutagenic. Mutagenesis is dependent on SOS processing of the lesions. The mutagenic spectrum depends on the repair background of the host cells. The role of repair in the mutagenesis of 3-HP-dUrd lesions is still unclear.
DNA adducts from in vivo inhalation exposure to tritiated PO - Analysis of exposures using concentration/response protocols demonstrated that there is a gradient in the binding of tritiated PO from the upper to the lower airways. Tritium content of DNA in nasal airway:trachea:lung = 6:2:1.

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STATUS: March 1993

DNA Adducts from In Vivo Inhalation Exposure to Tritiated PO: There appears to be a plateau concentration for the formation of DNA adducts in nasal, tracheal, and lung mucosa. Binding of tritiated PO to nasal cavity DNA decreases with biexponential kinetics. Initial phase is rapid. Clearance of PO adducts from trachea and lung is very slow.
Mutagenesis of single-stranded M13 DNA by PO: PO induces a higher frequency of base substitution mutations than frameshift or deletion mutations.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Solomon JJ

Publications, Abstracts, and Presentations supported by CIAR

1. Solomon JJ, F Li, F Mukai, and A Segal. 1991. Characterization and quantitation of in vitro DNA adducts of ethylene oxide. Hydroxyethylation at N-3 of cytosine results in a rapid hydrolytic deamination to a uracil adduct. Presented at Environmental Mutagen Society Annual Meeting, Orlando, FL. April 6-11.

2. Li F, A Segal and JJ Solomon. 1992. In Vitro Reaction of Ethylene Oxide with DNA and Characterization of Adducts. Chem Biol Interactions. 83:35-54.

3. Solomon JJ. 3-Hydroxyalkyl uracil: an epoxide-induced DNA lesion. Presented to Department of Pharmacological Sciences, State University of New York at Stony Brook, October 8, 1991.

4. Snow ET and JJ Solomon. 1992. Propylene Oxide Adducts at Cytosine Residues are Mutagenic Under SOS Conditions in E. Coli. Environmental Mutagen Society Annual Meeting, Reno/Sparks, NV, March 15-19, 1992. Abstract 14, Environ and Mol Mutagen, 19, Suppl. 20:59.

5. Solomon JJ, J Donahue, U. Singh, U Kher and OS Bhanot. 1992. Biological significance of alkylation at N3 of pyrimidines. Presented at the Gordon Research Conference on Mutagenesis, Plymouth State College, North Plymouth, NH, June 26-July 3.

6. Bhanot OS and JJ Solomon. 1993. The role of mutagenic metal ions in mediating in vitro mispairing by alkylpyrimidines. Invited lecture for the Second International Meeting on the Molecular Mechanisms of Metal Toxicity and Carcinogenicity, Madonna di Campilio, Italy, January 10-17.

7. Solomon JJ. 1992. DNA adducts of lactones, sultones, acylating agents and acrylic compounds. Invited chapter for IARC Monograph on DNA adducts of carcinogenic and mutagenic agents: chemistry, identification and biological significance.

8. Solomon JJ, US Singh and A. Segal. 1992. In vitro reactions of 2-cyanoethylene oxide with calf thymus DNA. Submitted to Chem.-Biol. Interactions.

9. Singh J., ET Snow and JJ Solomon. 1993. Propylene oxide induces SOS dependent mutagenesis at cytosines in single-stranded M13 DNA. Submitted for the 1993 annual meeting of the American Association for Cancer Research.

10. Bhanot OS, U Singh, U Kher and JJ Solomon. 1993. Ethylene oxide-induced N3-hydroxyethyl-deoxyuridine inhibits in vitro DNA replication. Submitted for the 1993 annual meeting of the American Association for Cancer Research.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Human Inhalability of Ultralarge Airborne Particles

PI: **David L. Swift, Ph.D.**
The Johns Hopkins University School of Hygiene & Public Health
Department of Environmental Health Sciences

This investigation proposes to test whether ultralarge particles (25-250 um diameter) are accessible to the nasal and oral airways and can deposit in these airways at sites which have acute or chronic health consequences, by carrying out controlled particle trajectory and deposition experiments at still or near still air flow conditions, first in mannikins and then in normal adult human subjects. The results of these experimental studies should be incorporated into dosimetric models and particle sampling protocols to provide a framework for predicting size related aerosol exposure effects for indoor environments.

Contract No.	93-02		
Contract Exec Date	2/2/93		
Contract End Date	2/2/94		
No Cost Extension			
Budget	$91,765	$95,814	$103,598
Budget Amendment			
Five month report due	7/2/93		
Five month report rec			
Site visit (anticipated)			
Site visit (conducted)			
Ten month report due	12/2/93		
Ten month report rec			
Continuation approved			

STATUS: MARCH, 1993

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

New Bioaerosol Sampling Techniques for Indoor Air Environments

PI: Klaus Willeke, Ph.D.
University of Cincinnati Medical Center
Department of Environmental Health

Portable personal and stationary area samplers with the same inlet and aerosol impaction stage will be developed, laboratory-evaluated, and field-tested to permit intercomparison of data on microorganism species identification and quantification of colony forming units.

Contract No.	90-16	90-16A	90-16B
Contract Execution Date	5/29/90	6/4/91	6/4/92
Contract End Date	5/29/91	6/4/92	6/4/93
No Cost Extension			
Budget	$171,335	$167,378	$184,599
Budget Amendment			
Five month report due	10/29/90	11/4/91	11/4/92
Five month report rec	11/09/90	11/18/91	11/9/92
Site visit (anticipated)			4/15/93
Site visit (conducted)	12/19/90		8/10/92
Ten month report due	3/29/91	4/4/92	
Ten month report rec	4/91	4/10/92	
Final report due			6/4/93
Final report rec			
Continuation approved			

STATUS: August 1991

Several commercially available bioaerosol samplers have been analyzed as to their operating principles and the different elements of the bioaerosol sampling process. Sampling efficiency has measured how well the inlet of a sampler draws in particles without being affected by the particles' sizes, shapes, velocities and travel directions. Collection efficiency has measured how well the sampler deposits the particles without being

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affected by their physical properties. Biological efficiency indicates the ability of the sampler to maintain the microbial viability and prevent cell damage during sampling.

Borrowing from techniques used in the fiels of industrial hygiene, the problems of quantitative bias due to statistical considerations, counting procedures, sample surface densities and sampling time can be minimized by using proper sampling procedures to obtain optimal samples. Guidelines for bioaerosol sampling have been revised and have been well-received at recent meeting presentations.

An easy-to-make virtual impactor has been developed to be utilized as an accessory to optical particle counters to optimize their sensitivity to larger particles. Work on the new design for the bioaerosol sampler, however, is progressing slowly, due to the optimal sampling times and optimal densities not being resolved as yet.

JANUARY, 1992

The PI has designed and built a sampler with three interchangeable inlets, which is being used to study the biological survival efficiency during sampling. Using the recently acquired biosafety hood, Pseudomonas fluorescens bacteria are nebulized and sampled by the new device. The experimental setup has been designed so that the biological viability can be studied for different stresses during impaction and different desiccation times after collection on the substrate. The number of incoming bacteria is counted by a laser-aerosol spectrometer (LAS). The number of bacteria that forms colonies on the substrate will be compared with the number of incoming bacteria from which the bacterial collection efficiency will be determined. Only a small fraction of the incoming bacteria is expected to be counted by the conventional colony-forming count technique. The results of this study may have a major impact on the interpretation of data from presently-available bioaerosol samplers and will provide design criteria for new ones.

In addition to the collection efficiency of available samplers, the PI is now studying the inlet efficiency of available samplers and is finding that there are considerable differences.

To avoid the collection of many inert dust particles for every microbe collected under normal sampling conditions, sampling times are often shortened. This attempt to prevent the masking of the microbes by the inert dust particles may result in a very low number of microbes in a given microscopic field. The PI currently is analyzing this effect with respect to any increase in the statistical uncertainty of the reported microbial counts. Project is essentially on schedule.

Associated Manuscripts and Abstracts/Presentations

1. "Performance of Bioaerosol Samplers: Collection Characteristics and Sampler Design Considerations," A. Nevalainen, J. Pastuszka, F.

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Source: https://www.industrydocuments.ucsf.edu/docs/hqhl0000

Liebhaber and K. Willeke, Atmospheric Environment, in print.

2. "Low-Cost Virtual Impactor for Large-Particle Amplification in Optical Particle Counters," F.B. Liebhaber, M. Lehtimaki and K. Willeke, Aerosol Science and Technology, 15:208-213, 1991.

3. "Bioaerosol Sampling," A. Nevalainen, K. Willeke, F. Liebhaber, J. Pastuszka, H. Burge and E. Henningson, in Aerosol Measurement: Principles, Techniques and Applications, K. Willeke and P. Baron (eds.), Van Nostrand Reinhold, New York, 1992.

4. "Bioaerosol Sampling," K. Willeke, in Guidelines for the Assessment of Bioaerosols with Indoor Environment, American Conference of Governmental Industrial Hygienists.

5. "Sampling for Bioaerosols: Simple Criteria for Comparing Sampler Performance," J. Pastuszka, A. Nevalainen, F. Liebhaber and K. Willeke, Abstract No. 222, American Industrial Hygiene Conference and Exhibition in Salt Lake City, Utah, May 18-24, 1991.

6. "Field Evaluations of Sampling Methods for Airborne Bacteria," A. Nevalainen and K. Willeke, Abstract No. 223, ibid.

7. "The Design of Field-Constructed Virtual Impactors Used for Sampling Aerosols," F.B. Liebhaber, M. Lehtimaki and K. Willeke. Abstract No. 327, ibid.

8. "Collection Characteristics of Bioaerosol Samplers," Pan-American Aerobiology Association Annual Symposium in Ann Arbor, Michigan, June 19-21, 1991.

9. "Sampling Time of Bioaerosol Samplers," F. Liebhaber, A. Nevalainen, J. Pastuszka, M. Thompson and K. Willeke, ibid.

10. "Application of Aerosol Sampling Techniques to Emerging Health Issues," K. Willeke, First Symposium on Pollution and Health Effects of Aerosols, Taipei, Taiwan, September 10-12, 1991.

11. "Sampling Times of Bioaerosol Samplers," F. Liebhaber, A. Nevalainen, J. Pastuszka, A. Juozaitis and K. Willeke, Abstract No. 11A.1, Annual American Association for Aerosol Research, Grand Traverse, Michigan, October 7-11, 1991.

12. "Collection Characteristics of Bioaerosol Samplers," K. Willeke, A. Juozaitis, A. Nevalainen, F. Liebhaber and J. Pastuszka, Abstract No. 11B.2, ibid.

13. K. Willeke, Annual Short Course on Bioaerosols in Ann Arbor, Michigan, October 28-30, 1991.

SEPTEMBER, 1992

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The focus on the physical aspects of bioaerosol sampling has included the aspiration of bioaerosols from the environment into an inlet, their transmission through the inlet, and efficient collection on a substrate within a relevant period of time that yields neither too high nor too low a particle density on the substrate for enumeration. This work has resulted in manuscripts on inlet efficiency, collection efficiency, sampling time, and the masking effect of deposited microorganisms.

After studying bioaerosol impaction with an experimental impactor, three new bioaerosol samplers have been designed and constructed: one with impaction onto a hard slide, one with impaction onto a soft agar medium, and one with impaction (also referred to as impingement) into a liquid. All three have the same impaction stage, consisting of a narrow 14.2 mm slot with a 60 degree tapered inlet, so that the physical sampling geometry is identical in each sampler. The slot width can be changed to 0.2, 0.3, and 0.4 mm.

The PI has been given a sabbatical leave to perform research in Munich, Germany, for two months in each of the three quarters of academic year 1992-93, starting September 1, 1992. He will collaborate with Professor R. Niessner of the University of Munich, who has been working on new methods of measuring indoor and outdoor pollutants, and also will visit and interact with other European institutions that are active in indoor research. In order to keep his research efforts going smoothly at the University of Cincinnati, Dr. Willeke specifically chose to be in Europe only for short intervals and thus will make three round trips to Europe, one per quarter. During his absence, Dr. Grinshpun will coordinate the research project and maintain it on schedule.

Associated Manuscripts and Abstracts/Presentations

1. Nevalainen, A., Pastuszka, J., Liebhaber, F. and Willeke, K. "Performance of Bioaerosol Samplers: Collection Characteristics and Sampler Design Considerations," Atmospheric Environment, 26A: 531-540 (1992).

2. Willeke, K., et al. "Application of Aerosol Sampling Techniques to Emerging Health Issues," Proceedings of the First Symposium on Pollution and Health Effects of Aerosols, Taipei, Taiwan, 508-515 (1991).

3. Willeke, K. "Characterization of Bioaerosol Samplers," lecture given at the EPA Research Center in Triangle Park, NC, December 18, 1991.

4. "Inlet Characteristics of Bioaerosol Samplers," in preparation for Journal of Aerosol Science.

5. "Universal Equation for Aerosol Aspiration from Calm and Moving Air," in preparation for Atmospheric Environment.

6. "Maximal Surface Density and Probability of Masking in Bioaerosol Microscope Counting," in preparation with Janet Macher and colleagues

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in Berkeley, California.

7. "Design and Performance of a New Bioaerosol Sampler for Indoor Air Environments," in preparation.

8. Thompson, M.W., Donnelly, J., Grinshpun, S.A., Juozaitis, A. and Willeke, K. "Method for Determining the Viable Fraction of Bioaerosols," submitted to American Industrial Hygiene Association Journal.

MARCH, 1993

With particular emphasis on the microbiological evaluation, the PI has applied the newly developed test methods to his new sampling devices and found optimal collection media as well as optimal sampling conditions for all three samplers.

The PI has conducted experiments first wuth biologically inert particles, and then with bacteria. All three of the new samplers were tested and then their performances were compared to those of several commonly used bioaerosol samplers. Collection efficiencies for all samplers were measured. The recovery of microorganisms was found to be superior with his impinger and agar slide impactor (close to 100%) than with the commercial devices tested.

With his methods of counting bioaerosol particles physically and simultaneously measuring their recovery after incubation, the PI was able to determine the bacterial recovery on an absolute basis. In addition, the comparison of the samplers' performances found with inert PSL particles to those found with bacteria of the same size enabled him to determine the survivability of microorganisms in bioaerosol samplers.

The newly-developed Agar Slide Impactor and the Liquid Impinger were tested in the field. Measurements of viable bioaerosol concentration were carried out in a variety of indoor air environments where different kinds of bioaerosol contaminants and different bacterial concentrations were expected. Most measurements were performed at the University of Cincinnati buildings (at the offices, auditorium, classroom, animal room, rest rooms, and laboratories). In addition, private homes were studied as well.

The analysis of the results obtained in the field study shows that the newly-designed Agar Slide Impactor and the Liquid Impinger demonstrated the higher number of recovered microorganisms than the commercial bioaerosol samplers used in the tests. This result was confirmed in a variety of environmental sites at various microbial concentrations. Furthermore, the counts obtained at the same environment with the UC Agar Slide Impactor and the UC Liquid Impinger were found to be approximately the same. Based on these results, the PI concludes that the field tests confirm the results of the previously conducted laboratory evaluation of the new bioaerosol samplers and proved their advantage over the commercial instruments. Project is on schedule.

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Associated Manuscripts and Abstracts/Presentations

1. Grinshpun, S.A., Chang, C.W., Juozaitis, A., Liebhaber, F., Thompson, M. and Willeke, K. "Sampling Efficiency of Bioaerosol Samplers," Abstract No. 293. American Industrial Hygiene Conference and Exhibition, Boston, MA, May 30-June 5, 1992, pp.85-86.

2. Chang, C.W., Grinshpun, S.A., Juozaitis, A., Liebhaber, F., Nevalainen, A., Thompson, M. and Willeke, K. "Inlet Sampling Efficiency of Bioaerosol Samplers," Symposium of the Pan-American Aerobiology Association, "Aerobiology 1992," University of Toronto, Scarborough, Canada, June 9-11, 1992.

3. Willeke, K., Grinshpun, S.A., Chang, C.W., Juozaitis, A., Liebhaber, F., Nevalainen, A. and Thompson, M. "Inlet Sampling Efficiency of Bioaerosol Samplers," European Aerosol Conference, Oxford, U.K., September 5-9, 1992.

4. Grinshpun, S.A., Chang, C.W., Kalatoor, S., Donnelly, J. and Willeke, K. "New Model of Inlet Sampling Efficiency and its Application to Bioaerosol Samplers," Abstract No. 3B.1. 11th Annual Meeting of the American Association for Aerosol Research, San Francisco, CA, October 12-16, 1992, p.88.

5. Willeke, K. Invited lectures at the Occupational Health Seminar, Yonsei University, Seoul, Korea and the International Aerosol Symposium, Ohta, Japan, August 1992.

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Neuroendocrine Lung Cancer: Mechanistic Studies

PI: Hanspeter R. Witschi, M.D.
University of California - Davis
Department of Veterinary Medicine

The investigators will analyze oncogene expression in lung cancers induced in hamsters during tumor development and in formed tumors. The understanding of early patterns of gene expression will allow for accurate prediction of ultimate tumor type.

Contract No.	90-24	90-24A	90-24B
Contract Execution Date	9/1/90	6/28/91	6/28/92
Contract End Date	9/1/91	6/27/92	6/27/93
No Cost Extension			
Budget	$166,099	$169,159	$179,200
Budget Amendment			
Five month report due	2/1/91	12/91	12/92
Five month report received	2/15/91	1/92	
Site visit (anticipated)			
Site visit (conducted)	5/20/91		
Ten month report due	7/1/91	5/92	FINAL 6/93
Ten month report received	5/30/91	9/92	
Continuation approved	6/28/91	9/92	

STATUS: August 1991

PI has been unable to produce small cell lung tumors in hamsters exposed to DEN and NNK (unable to reproduce results obtained in former work at Oak Ridge). PI has been able to produce adenomas and is proceeding with original work plan to investigate tumor formation mechanisms. PI has determined c-ki-ras expression using PCR technique, developed a new Northern blot protocol, tested p53 primers, and prepared RB primers for amplification of hamster cDNA.

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STATUS: January 1992

Serial sacrifice study with hamsters treated with NNK was begun in May. NNK injections and oxygen exposure were stopped 28 weeks later. Animals were sacrificed 3, 6, 9, 12, and 15 weeks after beginning treatment. No tumors were found in these groups. Determination of tumor incidence and harvesting of tumor material for molecular biological analysis from the longest exposed groups will occur in February. Investigators have developed a Northern blot methodology for their studies using a regenerating liver model.
The investigators have detected and confirmed the expression of Syrian Golden hamster c-Ki-ras 2 and p53 by amplification of reverse transcribed RNA extracted from fresh and frozen tissue, and by predicted size analysis, probing with a biotin labelled probe and by direct sequencing. In 6 NNK induced hamster non small cell lung cancer tumors examined, 50% were found to have c-Ki-ras 2 mutations at the 12th codon in the 2nd position. No mutations were found in the p53 message in any of the tumors examined.

STATUS: September 1992

Serial sacrifice study of hamsters treated with NNK - All animals had grossly visible lung tumors. Lung tumors of hyperoxia-exposed animals were smaller than air-exposed. From preliminary experiments with tissue from NNK treated hamsters, kept in air or in hyperoxia, NNK-induced carcinogenesis in the hamster results in characteristic alterations of Ki-ras but may not necessarily involve the p53 gene at this stage of tumorigenesis (28 - 40 weeks after the start of NNK administration).

STATUS: March 1993

Work designed to address original specific aim has been fully published in the open literature.
Having developed the techniques to discover point mutations in the K-ras oncogene, PI has begun to look for different K-ras mutations in lung tumors that grew under different conditions (different inducing carcinogens) or are presumably of different cellular origin. Experiments are underway in which two different strains of mice are treated with two different carcinogens (urethan and 3-methylcholanthrene). The different treatments and strains are expected to yield information on the specificity of K-ras mutations in murine lung tumors.

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Witschi HP

Publications, Abstracts, and Presentations supported by CIAR

1. Ning H, VIC Oreffo, PH Gumerlock, and H Witschi. 1991. Increased c-Ki-ras expression in hamster lung exposed to N-nitrosodiethylamine and hyperoxia as detected by polymerase chain reaction. Cancer Letters 59:75-80.

2. Oreffo VIC, PH Gumerlock and HP Witschi. 1991. Hamster ras family gene expression detected by the polymerase chain reaction. Abstract, Society of Toxicology 1991 Annual Meeting, Dallas, TX, Feb. 25 - Mar. 1.

3. Oreffo VIC, H Lin, PH Gumerlock, and HP Witschi. 1992. Detection of point mutations in hamster non small cell lung cancer induced by NNK. The Toxicologist 12:229.

4. Oreffo VIC, HW Lin, PH Gumerlock, SA Kraegel, and HP Witschi. 1992. Mutational analysis of a dominant oncogene (c-Ki-ras-2) and a tumor suppressor gene (p53) in hamster lung tumorigenesis. Molecular Carcinogenesis. 6:199-202.

5. Oreffo VIC, HW Lin, R Padmanabhan, and HP Witschi. 1993. K-ras and p53 point mutations in 4-(nitrosamino)-1-(3-pyridyl)-1-butanone induced hamster lung tumors. Carcinogenesis. In press (March issue).

6. Rajini PS, VIC Oreffo, HW Lin, and HP Witschi. 1993. Induction of K-ras mutations in hamster lung by 4-(nitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The Toxicologist 13:85 (1993 Annual SOT Meeting, New Orleans, LA).

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